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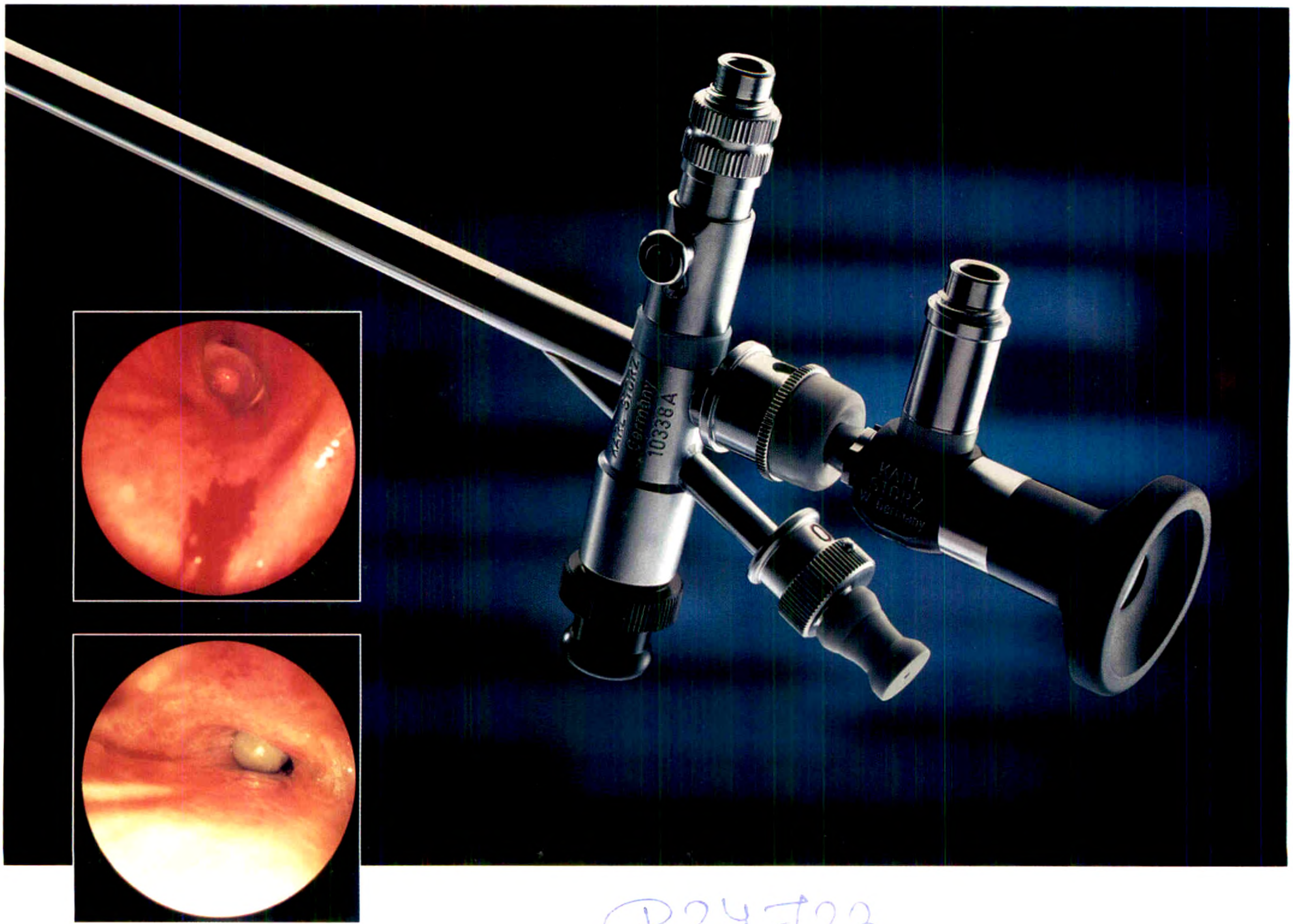

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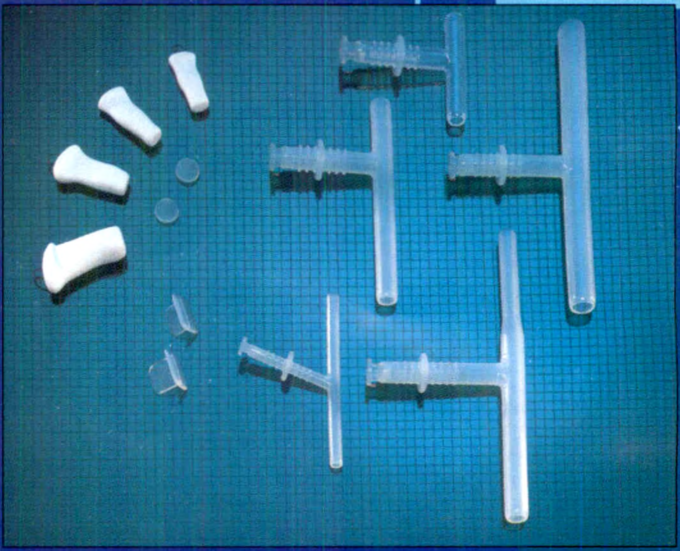

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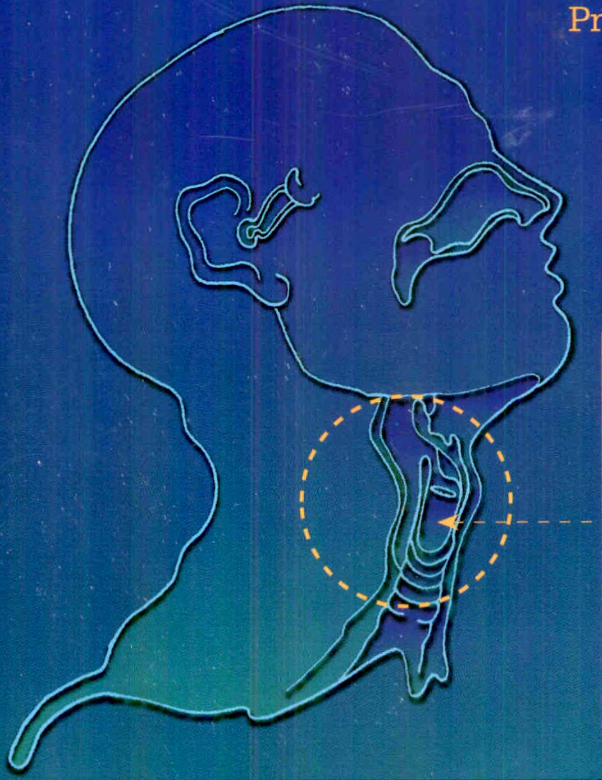

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FAILED EXTUBATION IN THE NEONATAL INTENSIVE CARE UNIT

PAUL WALKER, MBBS, FRACS
VITO FORTE, MD, FRCSC
TORONTO, CANADA

One of the roles of the pediatric otolaryngologist in the neonatal intensive care unit (NICU) is the assessment and management of the neonate who fails a trial of extubation. This paper reviews the recent 5-year institutional experience at The Hospital for Sick Children, Toronto, with neonates who failed extubation and who subsequently underwent diagnostic endoscopy. One hundred twenty-eight neonates from the NICU underwent diagnostic endoscopy. Of these, 58 neonates underwent diagnostic endoscopy for failure to extubate. Nine neonates were extubated after diagnostic endoscopy and retrial (16% of the series). Eleven neonates were extubated after additional endoscopic procedures (19% of the series). Twenty-four neonates underwent anterior cricoid split, of whom 20 or 83% (34% of the series) were eventually successfully extubated with no further airway intervention required during the study period (minimum 6 months' follow-up). Eleven neonates underwent tracheotomy (19% of the series). Four neonates underwent another external procedure to allow extubation (7% of the series). Three neonates died while still intubated (5% of the series). Our management of the neonate who fails a trial of extubation is discussed.

KEY WORDS — endoscopy, extubation failure, intensive care, neonate.

MATERIALS AND METHODS

The otolaryngological operating room surgical logbooks at the Hospital for Sick Children (HSC) from January 1987 to December 1991 were searched for all patients from the neonatal intensive care unit (NICU) who underwent diagnostic endoscopy or any other operative procedure. The hospital charts of these neonates were reviewed and the subgroup of neonates who underwent diagnostic endoscopy for failed extubation was identified. These charts were reviewed in detail to extract epidemiologic data including age, sex, race, gestational age, birth weight, reason for admission to the NICU with intubation, and gestational age at the date of first diagnostic endoscopy.

Otolaryngological intervention was recorded for each diagnostic or therapeutic procedure as date, endoscopic findings, additional operative procedures performed, recommendations made, and outcome. The endoscopic findings were grouped for analysis as acquired isolated glottic disorders, acquired combined glottic and subglottic disorders, acquired isolated subglottic disorders, and "other." The procedures performed were grouped for analysis as diagnostic endoscopy and retrial, additional endoscopic procedures (and retrial), anterior cricoid split (ACS), "re-do" ACS, and tracheotomy. Retrial was with or without corticosteroids and/or antibiotics. Gastroesophageal reflux on radiographic investigation was recorded but not analyzed, because documentation was uncertain.

Eventual outcome was determined. Successful extubation required no further airway intervention for the duration of the study or a minimum of 6 months, whichever was greater. Initial success was distinguished from later failure requiring reintubation. Whether successful extubation was accomplished on the first trial or on repeat trials was recorded. Data entry and analysis were performed on a personal computer with Quattro Pro version 3 (Borland International, Scotts Valley, Calif).

RESULTS

One hundred twenty-eight neonates who underwent diagnostic endoscopy from the NICU were identified. Of these, 58 (45%) underwent diagnostic endoscopy for failed extubation and are reported

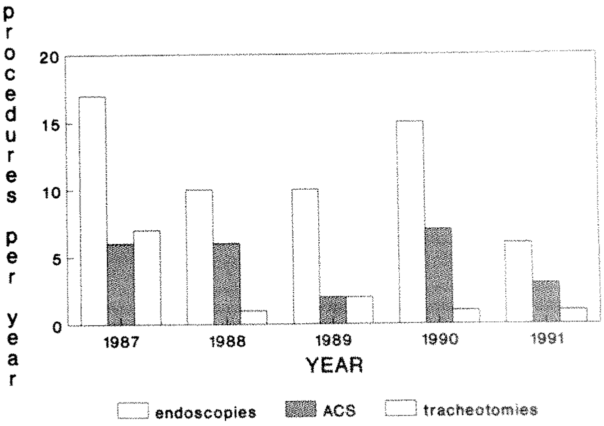

Fig 1. Number of procedures per year. ACS — anterior cricoid split.

From the Department of Otolaryngology, Hospital for Sick Children, University of Toronto, Toronto, Canada.

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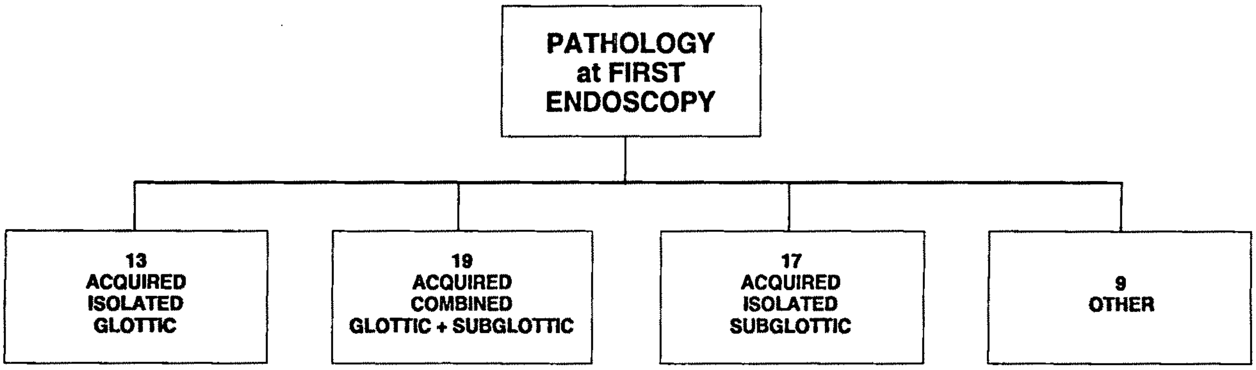

PATHOLOGY at FIRST ENDOSCOPY
13 ACQUIRED ISOLATED GLOTTIC
19 ACQUIRED COMBINED GLOTTIC + SUBGLOTTIC
17 ACQUIRED ISOLATED SUBGLOTTIC
9 OTHER

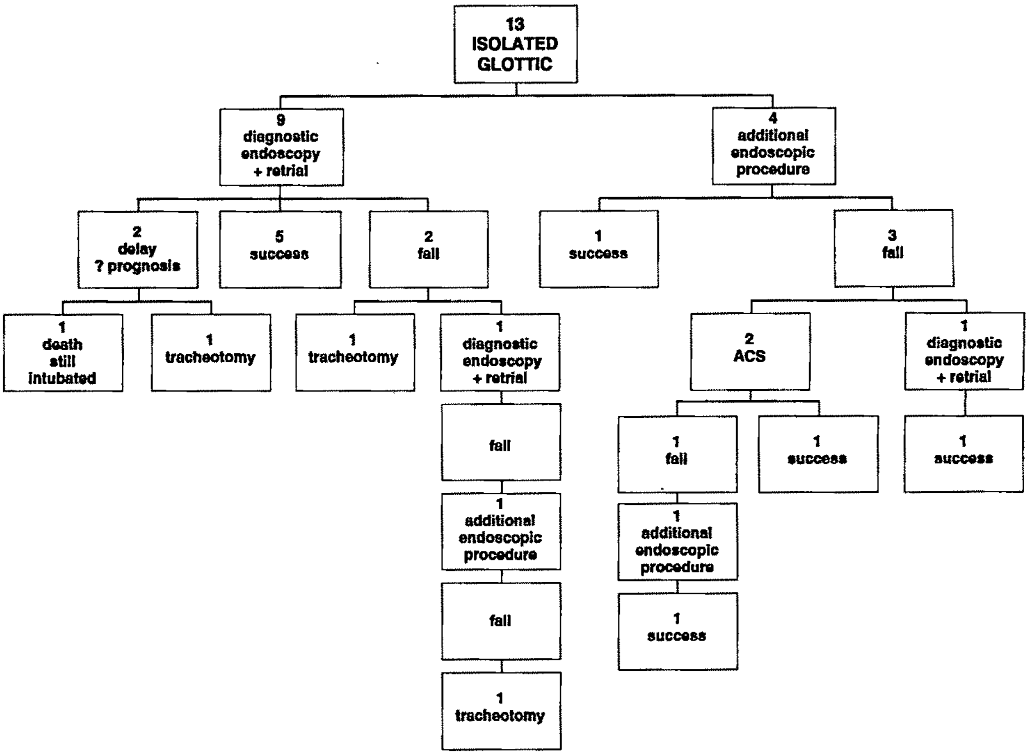
Fig 2. Results in terms of disorders encountered at first endoscopy.

here.

Thirty-five neonates were male (60%). Gestational age on admission to the NICU ranged from 23 weeks to 40 weeks (mean 29 weeks, sample SD 5.09). Birth weight ranged from 560 g to 4,800 g (mean 1,309 g, sample SD 975 g). The reason for intubation and admission to the NICU was most commonly respiratory distress due to bronchopulmonary dysplasia (in 47 or 81%), with the remaining neonates admitted for management of respiratory distress due to stridor at or soon after birth. The number of procedures per year of the study is depicted in Fig 1.

Thirty-four neonates (59%) underwent only a single diagnostic endoscopy for failure to extubate. Twenty-two underwent a second endoscopy, while 11 underwent 3 or more endoscopies. Gestational age at the time of first diagnostic endoscopy was a mean value of 39 weeks, with the youngest being 25 weeks of gestational age (chronologic age 9 days).

The results in terms of the disorders encountered at the first endoscopy are diagramed in Fig 2. The 9 neonates grouped together as "other" include 3 neonates with significant retrognathia who underwent tracheotomy at first endoscopy, 4 neonates who underwent a specific external procedure for extubation (1 diaphragmatic plication for hemidiaphragm paralysis, 1 innominate artery suspension, 1 wedge resection of tracheal diverticular cyst, and 1 excision of tracheal duplication cyst), 1 neonate who demonstrated only copious secretions (and subsequently died of severe bronchopulmonary dysplasia while still intubated), and 1 neonate who was described as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1 diagnostic endoscopy + retrial
fail
1 fail
1 success
1 success
1 additional endoscopic procedure
1 additional endoscopic procedure
fail
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1 tracheotomy

Fig 3. Procedures performed and outcome for acquired isolated glottic disorders.

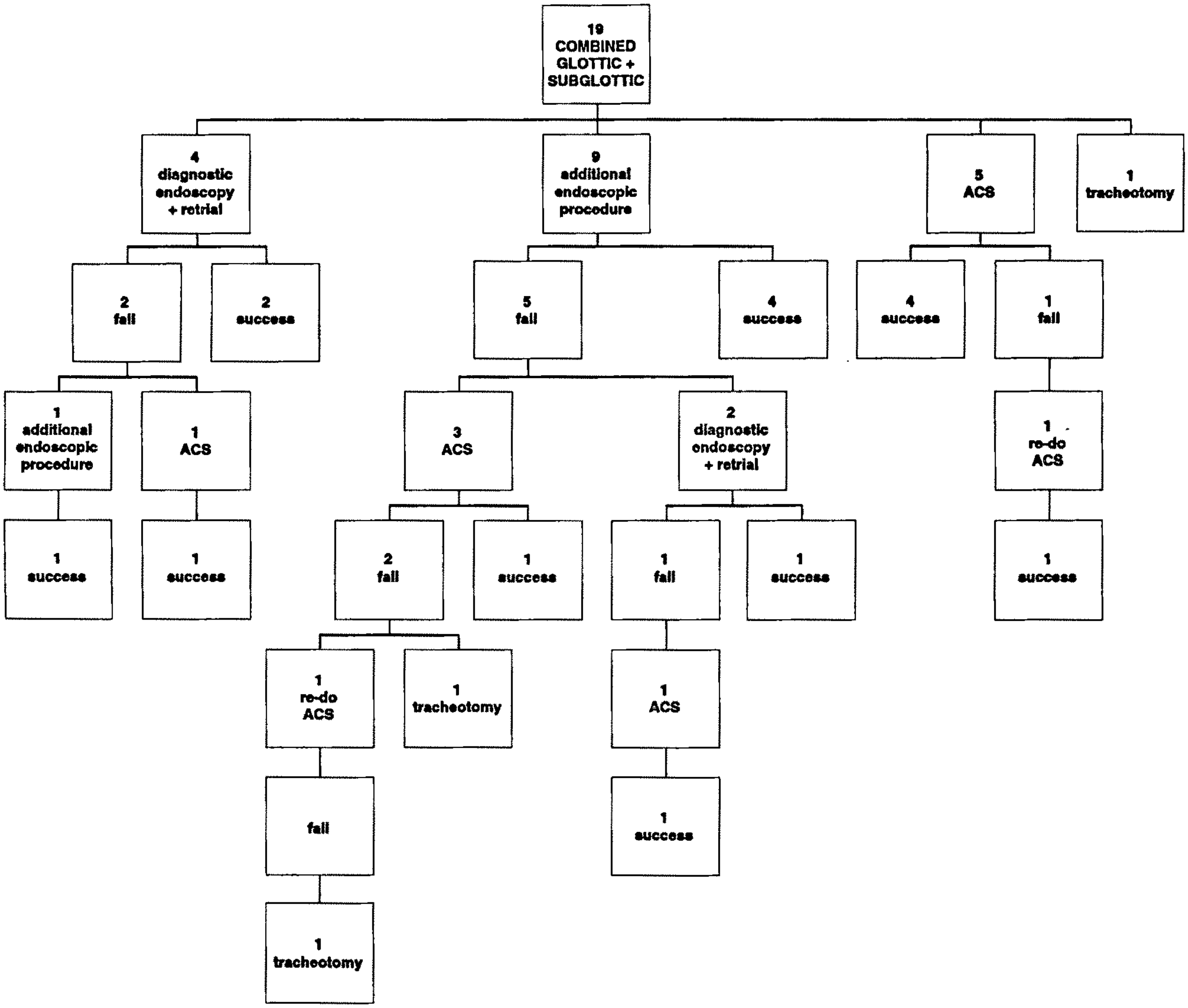

Fig 4. Procedures performed and outcome for acquired combined glottic and subglottic disorders.

having diffuse tracheobronchitis (extubated after retrial).

The procedures performed and their outcome for the 13 neonates with acquired isolated glottic disorders are diagramed in Fig 3. Tracheotomy was performed in 1 infant for prolonged ventilation due to severe underlying pulmonary disease and in 2 infants for severe laryngeal trauma following prolonged intubation.

The procedures performed and their outcome for the 19 neonates with acquired combined glottic and subglottic disorders are diagramed in Fig 4. Tracheotomy was performed in 1 neonate as an adjunct to management of multiorgan failure, in 1 (successfully extubated following an ACS) who required continuing doses of dexamethasone and developed a perforated duodenal ulcer, and in 1 following a failed re-do ACS.

The procedures performed and their outcome for the 17 neonates with acquired isolated subglottic disorders are diagramed in Fig 5. Tracheotomy was performed in 2 neonates following a failed ACS. One neonate had his diagnostic endoscopy abandoned because of anesthetic instability.

When failure occurred, it was noted within hours of extubation in the majority, but occasionally a neonate would be successfully extubated and then fail 4 to 6 weeks later.

The procedures that resulted in extubation are diagramed according to the level of disorder in Fig 6.

An ACS was performed in 24 neonates over the 5 years reviewed — 41% of the 58 neonates from the NICU who underwent diagnostic endoscopy for failed extubation. The mean gestational age on admission to the NICU was 27 weeks. The mean birth weight was 812 g. Thirteen of the infants were male (54%).

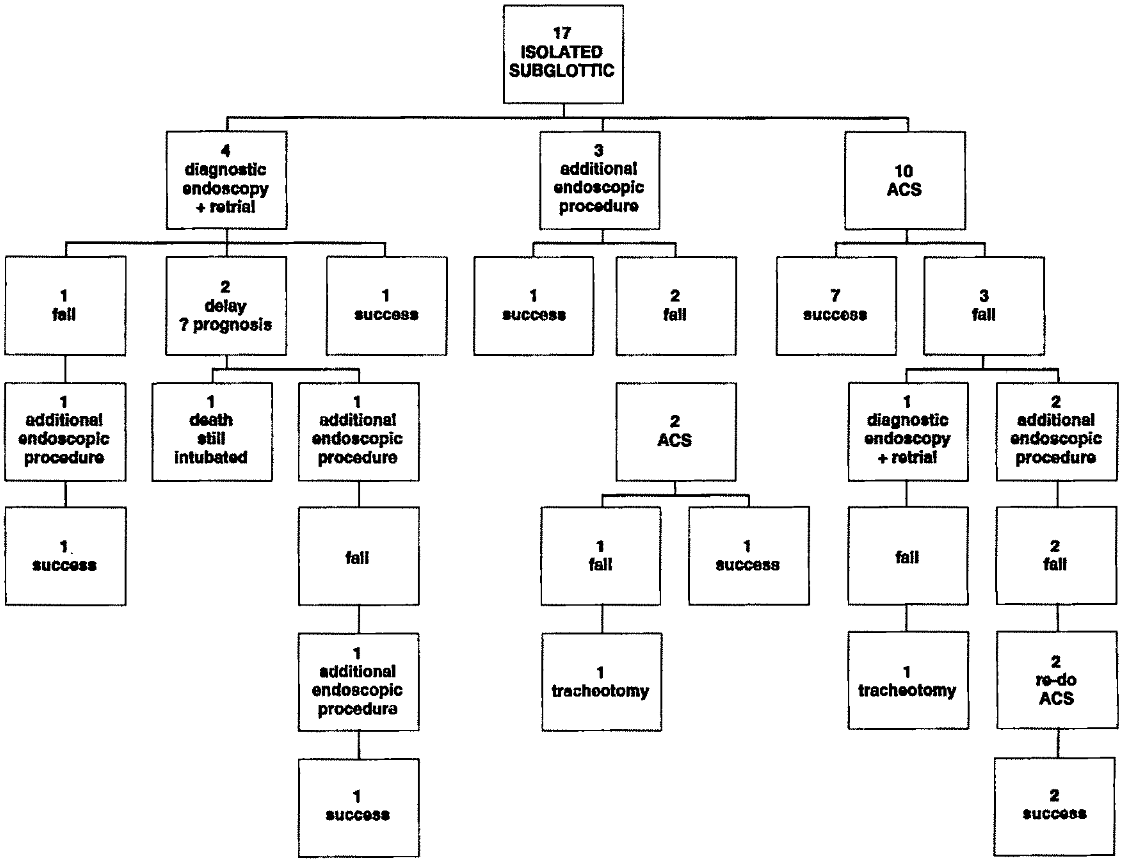
17 ISOLATED SUBGLOTTIC
4 diagnostic endoscopy + retrial
3 additional endoscopic procedure
10 ACS
1 fail
2 delay ? prognosis
1 success
1 success
2 fail
7 success
3 fail
1 additional endoscopic procedure
1 death still intubated
1 additional endoscopic procedure
2 ACS
1 diagnostic endoscopy + retrial
2 additional endoscopic procedure
1 success
fail
1 fail
1 success
fail
2 fail
1 additional endoscopic procedure
1 tracheotomy
1 tracheotomy
2 re-do ACS
1 success
2 success

Fig 5. Procedures performed and outcome for acquired isolated subglottic disorders.

Following an ACS (Fig 7), 16 neonates were successfully extubated with no further airway intervention for the duration of the study (minimum follow-up 6 months), including the 1 neonate who required continuing medical management for 11 days after extubation, prior to unexpected cardiac death.

Eight surviving neonates failed the ACS (33%). An additional endoscopic procedure was successful in 1. A re-do ACS was successful in 3 of 4. The fourth was successfully extubated, but required continuing dexamethasone and developed a perforated duodenal ulcer. To withdraw the dexamethasone and facilitate overall management, tracheotomy was performed. One neonate who underwent an ACS was prematurely extubated. This was the only complication of the ACSs in this series.

Overall, 20 neonates were successfully extubated after an ACS or a re-do ACS (83% of the 24 neonates who underwent an ACS), while 4 failed, requiring tracheotomy.

The outcomes that resulted in extubation for the 58 neonates who underwent diagnostic endoscopy after failure to extubate are diagramed in Fig 8. Nine neonates were successfully extubated after diagnostic endoscopy and retrial (16%). Eleven were extubated after additional endoscopic procedures (19%). Twenty were eventually extubated after an ACS (34%). Eleven underwent tracheotomy (19%). Four underwent another external procedure (7%) to allow extubation, and 3 died while still intubated (5%).

DISCUSSION

This paper reviews our experience with neonates who failed extubation in the NICU and who subsequently underwent diagnostic endoscopy. The timing of the decision to attempt extubation is made by the responsible neonatologists. At this time the medical or surgical condition requiring intubation should have resolved, the neonate should not require assisted ventilation, and he or she should not require supplemental oxygen at more than 35%. There should be no evident anatomic deformity likely to preclude successful extubation (in which case the otolaryngology service is involved at this stage). We do not consider the presence or absence of an audible leak around the tube to be prognostic.

After initial failure to extubate due to airway obstruction at or below the larynx, the neonate receives dexamethasone at our recommended dose of 1 mg/kg every 8 hours for 48 hours prior to and following a second trial of extubation. After extubation,

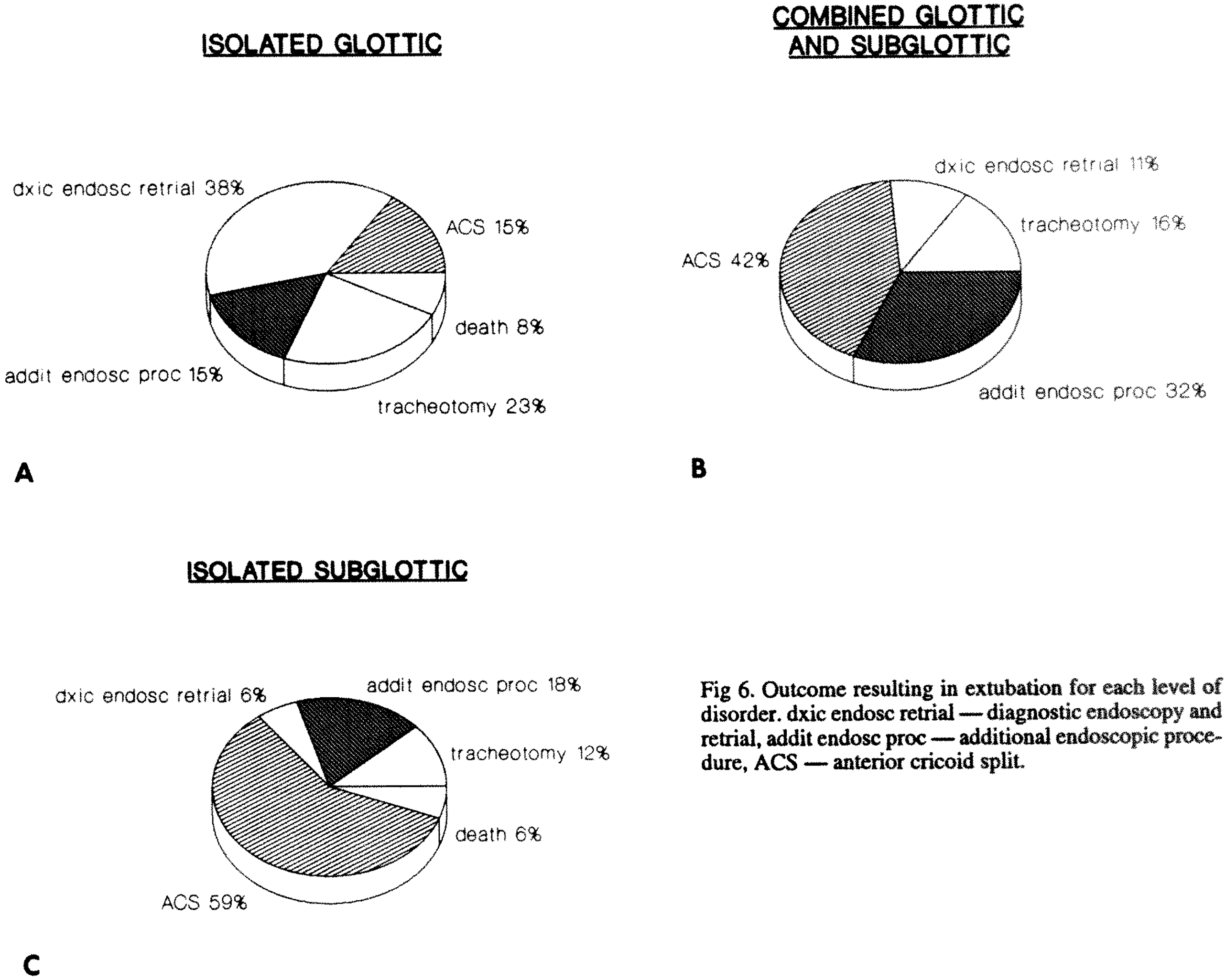

Fig 6. Outcome resulting in extubation for each level of disorder. dxic endosc retrial — diagnostic endoscopy and retrial, addit endosc proc — additional endoscopic procedure, ACS — anterior cricoid split.

racemic epinephrine is delivered as required within the limits of dose-related tachycardia. Heliox is also used as necessary.

If the neonate fails again, then the otolaryngology service evaluates the patient. The past medical and surgical history is reviewed. The nature and timing of the failure to extubate are elicited, and the effect of any specific maneuvers (eg, insertion of a nasopharyngeal airway) is determined.

Specific examination evaluates the adequacy of the nasal airway, the midfacial dimensions, and the anatomy of the oral cavity, oropharynx, and neck to exclude an obstruction above the larynx or extrinsic compression of the airway. The anteroposterior and lateral chest x-ray films are reviewed.

A proportion of the neonates we are asked to see have significant nasal obstruction, due most commonly to an irritative rhinitis secondary to prolonged nasal intubation, and often with a nasogastric tube down the other nostril. Since the neonate is an obligate nasal breather, he or she may fail a trial of extubation. The diagnosis may be confirmed via passage of a telescope into the anterior nares. Management includes replacement of any nasal tube with oral tubes for 48 to 72 hours plus topical nasal instillation of a combination antibiotic-corticosteroid-vasoconstrictor drop 3 or 4 times daily, followed by another trial. If extubation is successful, then the nasal drops are continued another day or two. On occasion the obstruction is bypassed by the passage of a nasopharyngeal airway to a level that relieves the obstruction. The position of the tube is carefully noted and topical drops are continued.

Less commonly, midfacial disproportion is identified. Our initial management is the same, but failure of the trial of extubation is more likely. If bony nasal cavity stenosis or posterior choanal stenosis is thought probable, then a CT scan is performed. Endoscopic evaluation follows, both to exclude an additional airway anomaly and to allow dilation and stent placement.

After our review the next trial of extubation is arranged for a time at which we can be present. Accumulation of subglottic edema after removal of

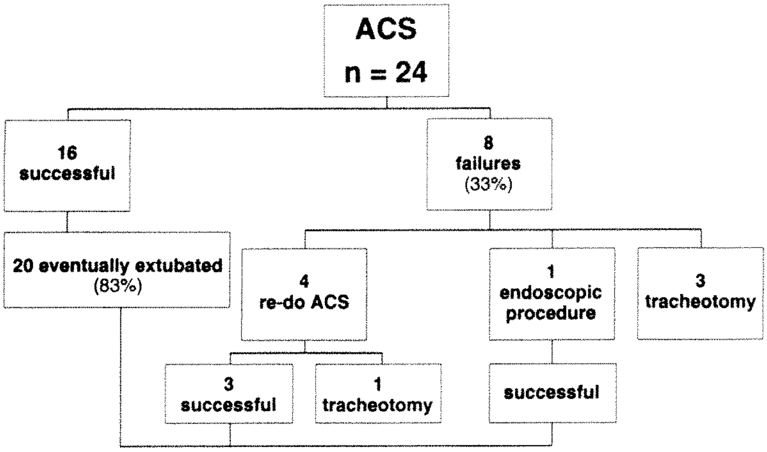

Fig 7. Outcome of anterior cricoid split (ACS).

the stenting effect of the endotracheal tube may take some hours to develop, with failure of the trial some hours after extubation. If the neonate fails yet again, we occasionally recommend delay and further trial, but usually proceed to diagnostic endoscopy. This is the subgroup reviewed here. Diagnostic endoscopy in this age group is more demanding than in any other because of the narrower margins for oxygenation of the neonate. Diagnostic endoscopy on neonates from the NICU is always performed in the operating room.

At the time of endoscopy, specific evaluation is made for congenital obstructive lesions, as well as for evidence of damage caused by the endotracheal tube. In this study multiple factors contributing to a failure to extubate were identified in the majority. The most likely cause of failure to extubate is acquired subglottic stenosis. In a prospective study of 289 premature infants weighing less than 1,500 g at HSC,[1] subglottic stenosis was found to be an uncommon complication of prolonged intubation in the NICU, being identified in 2.6%. With increased awareness in the NICU of the potential for subglottic stenosis due to endotracheal tube trauma, it may be expected that the number of acquired subglottic stenoses will be reduced, and this is partially reflected in the declining numbers of diagnostic endoscopies required each year in this study (Fig 1). Although the number of tracheotomies required may be declining, the number of ACSs performed remains fairly steady.

We assess the caliber of the subglottis visually and by the difficulty of passage of the 2.5-mm Storz bronchoscope (coupled with Hopkins rod telescopes), and by the site(s) and extent of mucosal edema, erythema, erosions or ulcerations, granulation tissue, and cartilage exposure. It is important to allow sufficient time for edema within the subglottis to develop after removal of the stenting effect of the endotracheal tube.[2] Typically, early subglottic mucosal damage is maximal posterolaterally.[3] Subglottic ductal cysts are amenable to laser deroofing.

If the caliber of the subglottis appears adequate but there is obstructing granulation tissue at the glottis, which most commonly arises from the vocal processes of the arytenoids, this is excised or lasered.

Bilateral vocal cord palsy may be suspected clinically with a history of stridor from birth together with immediate failure of a trial of extubation but "easy" reintubation. Subtle vocal fold motion abnormalities may be difficult to appreciate in the inflamed and edematous glottis.

The overall rate of extubation following ACS and re-do ACS in this study of 83% (Fig 6) compares favorably with published success rates of 43% to 80% for similar study groups from NICUs without previous tracheotomy.[2,4-8] We do not regard adding an interposition graft[8] as advantageous. When planning the incision for an ACS we site the transverse incision approximately one quarter the distance from the cricoid to the suprasternal notch, thus allowing the same incision to be used if tracheotomy becomes necessary.

Our flowchart of recommended management for failure to extubate from the NICU is shown in Fig 9. Our results for each level of disorder are diagramed in Fig 6.

For isolated acquired glottic disorders due to edema,

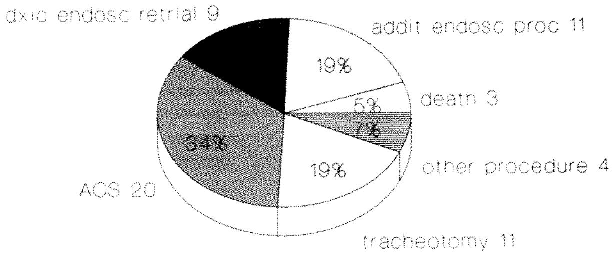

Fig 8. Outcome that resulted in extubation. dxic endosc retrial — diagnostic endoscopy and retrial, addit endosc proc — additional endoscopic procedure, ACS — anterior cricoid split.

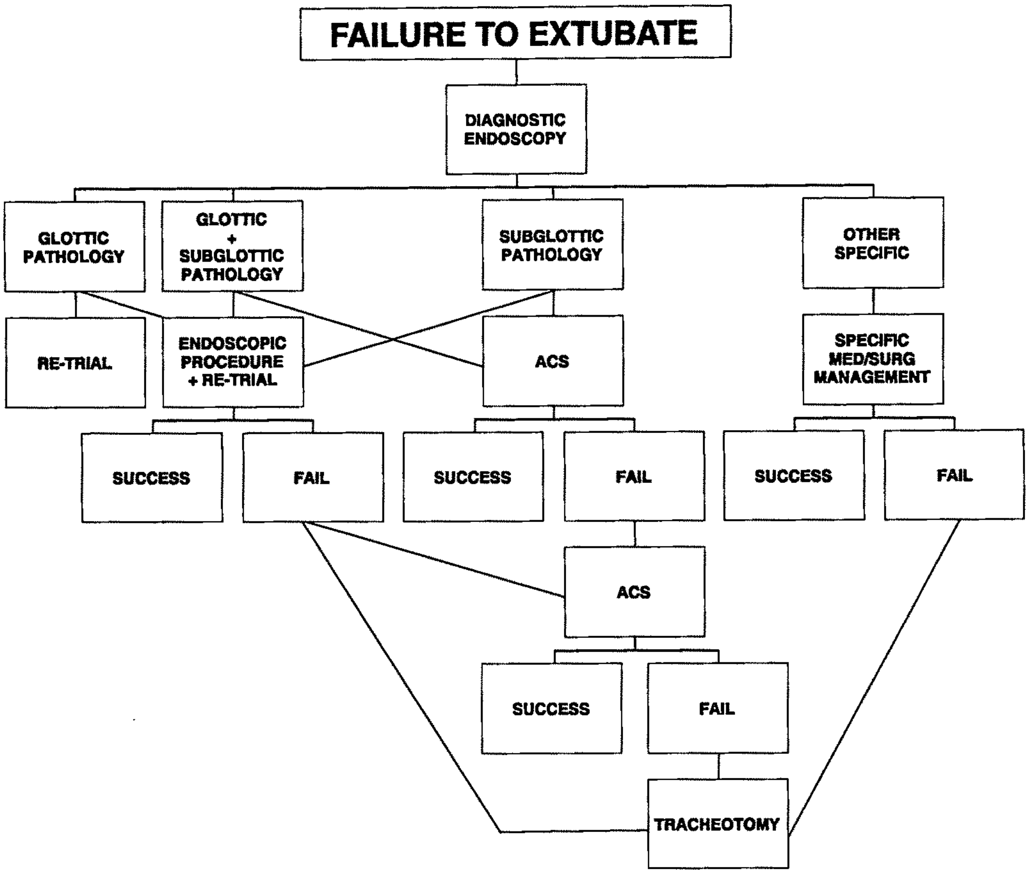

Fig 9. Flowchart of recommended management for failure to extubate. ACS — anterior cricoid split.

retrial with steroids and/or antibiotics is appropriate. For isolated acquired glottic disorders suitable for endoscopic laser treatment (eg, granulation tissue), we laser endoscopically and perform a retrial. In the event of failure, the severity of laryngeal damage is reassessed and tracheotomy is performed if severity warrants. If the damage is not too severe, we proceed to an ACS.

For combined acquired glottic and subglottic disorders, we judge which lesion appears the more significant. If the glottic lesion predominates, we proceed as for an isolated glottic disorder, with the rationale that success or failure following retrial will be known within a few days — thus possibly sparing the larynx the further intubation associated with the ACS. If the subglottic lesion appears most significant, we proceed either to endoscopic laser treatment if the disorder is suitable (eg, subglottic "soft" granulation tissue or subglottic cysts) or to an ACS if it is not suitable for laser treatment.

Following a failed ACS for a subglottic disorder, a re-do ACS is indicated. If a re-do ACS fails, luminal augmentation with an interposition graft is possible, although to date we have proceeded to tracheotomy.

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TRANSIENT HYPOCALCEMIA AFTER THYROIDECTOMY

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The causes of transient hypocalcemia after thyroid surgery are not fully understood. In 95 consecutive patients undergoing total thyroidectomy (n = 30), subtotal thyroidectomy (n = 14), or hemithyroidectomy (n = 51), we serially measured total calcium, parathyroid hormone (PTH), and proteins before surgery and 6, 24, 48, 72, and 96 hours after surgery, and we calculated the corresponding ionized calcium levels. In the whole population, there was a statistically significant decrease of PTH, total calcium, and proteins at nearly every time of blood withdrawal, when compared with the preoperative levels. The PTH decreased earlier and total calcium levels were significantly lower after total thyroidectomy than after hemithyroidectomy (at 48, 72, and 96 hours). Ten patients had on 2 occasions serum calcium levels below or equal to 2 mmol/L and were defined as having severe hypocalcemia. Severe hypocalcemia was found in 8 patients after total thyroidectomy, compared with 2 after hemithyroidectomy ($p < .05$), and was present in 3 of the 5 patients with thyroid carcinoma, compared with 7 of the 90 patients with nonmalignant thyroid diseases ($p < .01$). Despite careful preservation of the parathyroid glands and their blood supply, thyroidectomy was often followed by transient hypocalcemia, the determinants of which are hypoparathyroidism and hemodilution. No patients had persistent symptoms of hypocalcemia from 2 to 3 months after surgery.

KEY WORDS — calcium, hypoparathyroidism, parathyroid hormone, thyroidectomy.

The pathogenesis of transient hypocalcemia after thyroid surgery is not fully understood. It has been reported to occur more commonly after total thyroidectomy (from 6.9% to 25%)[1-3] than after subtotal thyroidectomy (from 1.6% to 9.1%)[1,2,4] or hemithyroidectomy.[5,6] Permanent hypocalcemia, which could be defined as a hypocalcemia lasting 2 months or more after thyroid surgery, is due to vascular necrosis and/or accidental removal of the parathyroid glands. It occurs more frequently after total thyroidectomy (from 0.4% to 13.8%)[1-3,7-11] than after bilateral subtotal thyroidectomy (from 0.2% to 1.9%).[2,4] Thus, some surgeons became reluctant to perform total thyroidectomy because of the risk of permanent damage to the parathyroid glands. Such incomplete thyroid surgery may compromise patient management. Moreover, it should be pointed out that in several recent prospective studies, permanent hypocalcemia never happened.[5,12]

The initial goal of our study was to follow the evolution of serum concentrations of calcium and parathyroid hormone (PTH) during the first 4 days after thyroid surgery, in order to determine if early temporary hypocalcemia would be predictive of permanent hypocalcemia. Actually, we found that this was not the case.

PATIENTS AND METHODS

Ninety-five patients (17 men and 78 women) undergoing thyroid surgery (including 30 patients undergoing total thyroidectomy, 14 subtotal thyroidectomy, and 51 unilateral lobectomy) were prospectively followed. Their ages ranged from 23 to 71 years, with a mean age ± SD of 45.5 ± 11.8 years. Five patients had thyroid carcinoma (all of them underwent total thyroidectomy), 30 patients had multiheteronodular goiter (23 underwent total thyroidectomy and 7 subtotal thyroidectomy), 6 patients had Graves' disease (all of them underwent subtotal thyroidectomy), 7 patients had a preoperative diagnosis of toxic solitary nodule (1 of them underwent subtotal thyroidectomy and the remaining 6 unilateral lobectomy), and 47 patients had a cold nodule (2 of them underwent total thyroidectomy because of a suspicion of malignancy on the extemporaneous histologic examination and the remaining 45 had unilateral lobectomy).

Surgical Techniques. Surgical techniques were identical for every operation. After making an incision in the lower anterior neck and after dissecting the subhyoid muscles (without cutting them), the thyroid gland was exposed and the thyroid capsule was dissected. Whereas the inferior laryngeal nerves were systematically searched for, the parathyroid glands were not, but they were usually exposed during dissection. When one of the parathyroid glands was thought to be devascularized (according to macroscopic aspect — modification of size or color — or in case of section of its pedicle), this gland was cut into a dozen pieces and then reimplanted in a small cavity

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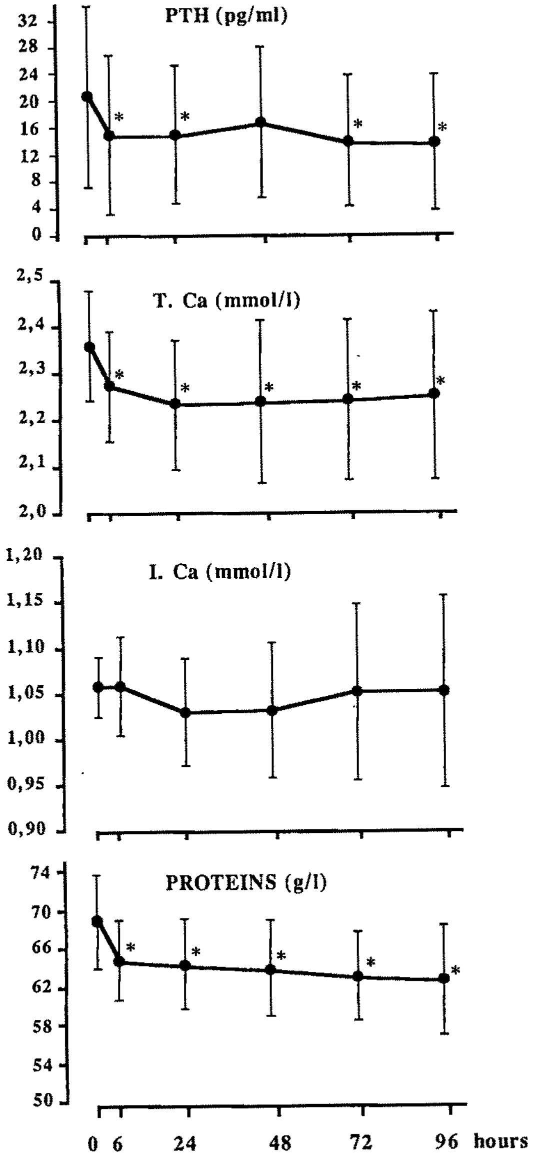

Fig 1. Time evolution of serum parathyroid hormone (PTH), total calcium (T. Ca), calculated ionized calcium (I. Ca), and proteins for whole population (mean ± SD). Asterisks — statistical significance versus preoperative value (ANOVA followed by Scheffé's tests).

made in the sternocleidomastoid muscle. Hemithyroidectomy consisted of total lobectomy plus isthmectomy. In case of subtotal thyroidectomy, we only preserved a small slice of posterior gland tissue on each side, or a small piece of each superior pole of the thyroid gland. Among the 30 patients who underwent total thyroidectomy, reimplantation of a single parathyroid gland was performed in only 4.

Study Protocol and Laboratory Evaluation. Serum concentrations of total calcium (protein-bound and free), proteins, and PTH were determined just before (H0) and 6 (H6), 24 (H24), 48 (H48), 72 (H72), and 96 (H96) hours after surgery. Free or ionized calcium was calculated according to the following formula[13]:

$$Ca^{++}\ (\text{mmol/L}) = [240 \times \text{total calcium (mmol/L)} - \text{proteins (g/L)}/3]/4 \times [\text{proteins (g/L)} + 60]$$

Total calcium level was determined by the standard spectrophotometric method of calcium binding to orthocresolphthalein complexone, using an automated analyzer (Dimension, Du Pont de Nemours). Normal values for our laboratory range from 2.1 to 2.6 mmol/L. Total proteins were determined by the standard photometric biuret method and expressed in grams per liter. Serum levels of intact human PTH (1 to 84) were determined by an immunoradiometric assay (INCSTAR Corp, Stillwater, Minn), with an interassay coefficient of variation (CV) of 10.8% for a serum level of 12 pg/mL, an intraassay CV not exceeding 15% in the normal range of PTH values (10 to 50 pg/mL for our laboratory), and a detection threshold of 1 pg/mL.[14,15] In addition, serum thyrocalcitonin was determined in 36 patients, by an immunoradiometric assay (CIS bio international, Gif-Sur-Yvette, France).

Statistical Analysis. One-way analysis of variance (ANOVA) for repeated measures was performed to study the evolution of each parameter at different times. Between-groups comparison of each parameter was achieved with a 1-way ANOVA. The ANOVAs were followed when necessary by Scheffé's tests for contrast analysis. Observed frequencies of events were compared by means of a χ^2 test, adjusted when necessary for low numbers of patients (Yates correction). All statistical assessments were based on 2-tailed tests. All results are expressed as means ± SD; $p \leq .05$ was considered significant.

RESULTS

The overall time evolution of PTH, total calcium, ionized calcium, and proteins is shown in Fig 1. The lowest value for mean PTH occurred at H96 (13.5 ± 10.0 pg/mL), but when compared (by ANOVA for repeated measures) to the mean baseline preoperative value (20.5 ± 13.5 pg/mL), PTH levels were significantly lower at any time of determination, except H48. Similarly, mean total calcium levels were significantly lower than the mean baseline value (2.37 ± 0.09 mmol/L) at any time of determination, with a nadir value at H24 (2.24 ± 0.14 mmol/L). Calculated ionized calcium did not show a significant decrease at any time of determination. Serum proteins showed a fast significant decrease from H0 (69.2 ± 4.9 g/L) to H6 (65.0 ± 4.2 g/L), followed by a slower decrease from H6 to H96 (62.9 ± 5.8 g/L). There was a weak but significant positive correlation between the individual values of calcium H48 and

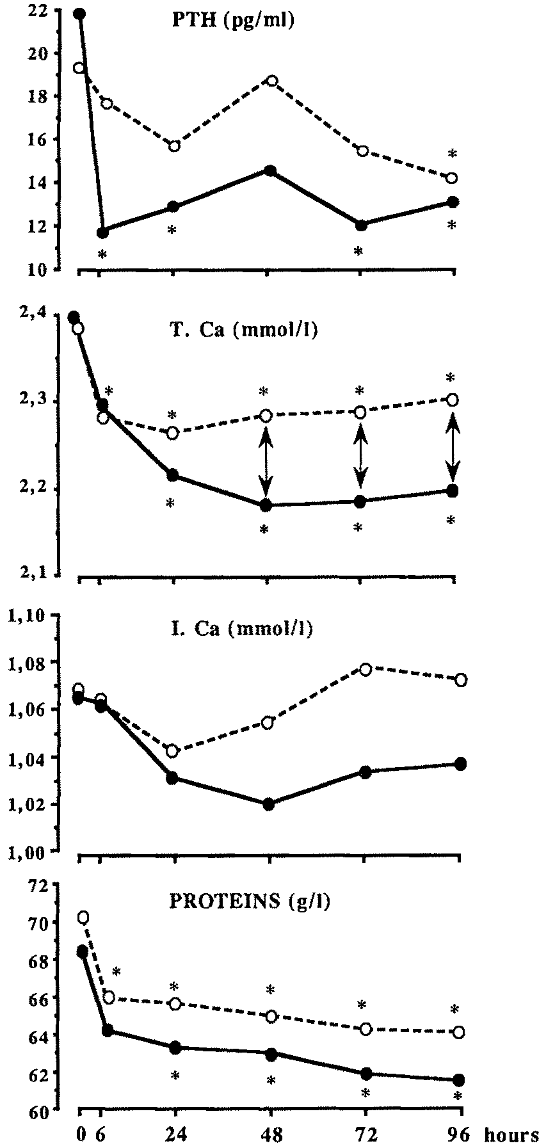

Fig 2. Comparative time evolution of serum parathyroid hormone (PTH), total calcium (T. Ca), ionized calcium (I. Ca), and proteins in patients who underwent total thyroidectomy (TT; closed circles and solid lines) or hemithyroidectomy (HT; open circles and dotted lines). Asterisks — statistical significance versus preoperative (H0) value, arrows — statistical significance between values for TT and for HT.

PTH H48, calcium H72 and PTH H72, calcium H96 and PTH H96, and between individual nadir values for calcium and PTH (all r = .3; all p < .05).

Total Thyroidectomy. When compared with the mean basal H0 value (21.6 ± 16.2 pg/mL), PTH was found to be significantly lower at any time except H48. The nadir was observed at H6 (11.8 ± 12.8 pg/mL). Compared with the basal H0 value (2.38 ± 0.10 mmol/L), total calcium was significantly lower at times H24, H48, H72, and H96, with a nadir value at H48 (2.18 ± 0.21 mmol/L), followed by a plateau (see Table and Fig 2). Calculated ionized calcium was lower than baseline H0 values (1.07 ± 0.04 mmol/L) at any time, the nadir being reached at H48 (1.02 ± 0.08 mmol/L), but this trend was not statistically significant. Proteins showed a fast, significant fall from H0 (68.2 ± 4.9 g/L) to H6 (64.2 ± 4.0 g/L), followed by a slow decrease. Values at H24, H48, H72, and H96 were significantly lower than the preoperative level. The lowest value was H96 (61.5 ± 6.4 g/L).

Subtotal Thyroidectomy. Subtotal thyroidectomy was not followed by a significant decrease of any parameter at any time, the main reason being the small size of this cohort, due to numerous missing values (data not shown).

Hemithyroidectomy. When compared with mean basal H0 value (19.3 ± 9.9 pg/mL), serum levels of PTH at times H6, H24, H48, H72, and H96 were lower, but the only significant difference was found at H96 (14.1 ± 8.2 pg/mL). Total calcium dropped significantly from H0 (2.38 ± 0.10 mmol/L) to H6 (2.28 ± 0.12 mmol/L) and then reached a plateau, the level of which was significantly lower than baseline (see Table and Fig 2).

Comparison Between Total Thyroidectomy and Hemithyroidectomy. Comparative evolution of all serum parameters is shown in Fig 2. Values of the different parameters were always lower after total thyroidectomy than after unilateral lobectomy, but the difference usually did not reach statistical significance because of large interindividual variations. However, total calcium was significantly lower (p < .05) after total thyroidectomy than after hemithyroidectomy at times H48, H72, and H96 (2.16 ± 0.21 mmol/L versus 2.27 ± 0.12 mmol/L, 2.17 ± 0.21 mmol/L versus 2.29 ± 0.14 mmol/L, and 2.19 ± 0.24 mmol/L versus 2.31 ± 0.10 mmol/L, respectively).

It should be noticed that after total thyroidectomy, the early decrease of PTH occurred before the maximal decrease of total calcium, whereas after hemithyroidectomy, the decrease of PTH followed that of total calcium, and happened later than after total thyroidectomy.

The individual nadirs of PTH and total calcium were determined in every patient. In patients who underwent total thyroidectomy, the mean PTH nadir was lower than in those who underwent hemithyroidectomy (7.2 ± 6.7 pg/mL versus 11.3 ± 8.1 pg/mL; p < .05). Similarly, the means of individual total calcium nadirs and ionized calcium nadirs were significantly lower after total thyroidectomy than after hemithyroidectomy (2.10 ± 0.21 mmol/L versus 2.20 ± 0.13 mmol/L for total calcium and 0.97 ± 0.10 mmol/L versus 1.02 ± 0.07 mmol/L for ionized cal-

EVOLUTION OF SERUM PARATHYROID HORMONE AND TOTAL CALCIUM DURING FIRST 96 HOURS AFTER THYROID SURGERY

		H0	*H6*	*H24*	*H48*	*H72*	*H96*
Total thyroidectomy	PTH (pg/mL)	21.6 ± 16.2	11.8 ± 12.8	12.8 ± 10.8	14.5 ± 12.1	12.0 ± 9.4	13.0 ± 12.6
	T.Ca (mmol/L)	2.40 ± 0.10	2.29 ± 0.12	2.22 ± 0.15	2.18 ± 0.21*	2.19 ± 0.22*	2.20 ± 0.24*
Hemithyroidectomy	PTH (pg/mL)	19.3 ± 9.9	17.7 ± 11.2	15.7 ± 9.2	18.7 ± 10.8	15.4 ± 10.4	14.1 ± 8.2
	T.Ca (mmol/L)	2.38 ± 0.10	2.28 ± 0.12	2.26 ± 0.14	2.28 ± 0.14	2.29 ± 0.13	2.30 ± 0.10

Data are mean ± SD.

PTH — parathyroid hormone, T.Ca — total calcium, H0 — preoperatively, H6 — 6 hours after surgery (etc).

*Statistically significant difference between corresponding values after total thyroidectomy and hemithyroidectomy (analysis of variance).

cium; $p < .05$).

We chose to define severe hypocalcemia as a serum calcium concentration less than or equal to 2 mmol/L at 2 different times of blood withdrawal. Using this criterion, 10 patients were selected: 8 of them had undergone total thyroidectomy and the remaining 2 unilateral lobectomy. The proportion of severe hypocalcemia was significantly higher after total thyroidectomy than after hemithyroidectomy (8 of 30 versus 2 of 51; $\chi^2 = 7.07$; $p < .01$). These 10 patients also had significantly lower levels of PTH. Symptoms of hypocalcemia were found in 12 patients, including the 10 aforementioned as having severe hypocalcemia. We also selected patients whose nadir of PTH was inferior or equal to 2 pg/mL; 9 had undergone total thyroidectomy, none subtotal thyroidectomy, and only 2 hemithyroidectomy. Again, the proportion of severe hypoparathyroidism was significantly higher after total thyroidectomy than after hemithyroidectomy ($\chi^2 = 8.72$; $p < .01$).

Influence of Disease. The proportion of severe hypocalcemia as previously defined was significantly higher in patients with thyroid carcinoma than in patients with other thyroid diseases (3 of 5 versus 7 of 90; $\chi^2 = 8.65$; $p < .01$). An obvious explanation for this discrepancy is the search for and removal of recurrent adenopathies during surgery for carcinoma, implying an increased risk of parathyroid injury. However, our pathologists never found any parathyroid gland in the surgical specimens of these cases.

Long-term Evolution. It should be stressed that none of our patients, even those with severe transient hypocalcemia, had clinical symptoms of permanent hypocalcemia 2 to 3 months after surgery.

DISCUSSION

We found a significant decrease of both PTH and total calcium serum levels during the 4 days following thyroid surgery. However, only 12 patients among the 95 studied had clinical symptoms of hypocalcemia, including 10 with severe hypocalcemia (≤2 mmol/L on 2 occasions). Not surprisingly, these patients had a calculated ionized calcium significantly lower than that of the remaining population at any time of determination. Since no patient had permanent symptoms of hypocalcemia 2 to 3 months after surgery, transient and permanent hypocalcemia appear as 2 distinct phenomena, the former not being predictive of the latter. On the latest blood sample (H96), serum levels of PTH, calcium, and proteins were still significantly lowered when compared with H0, so that a more prolonged period of observation would have been necessary to fully describe the evolution of these parameters after thyroid surgery.

Several causes for transient postthyroidectomy hypocalcemia have been suggested. Ischemia of the parathyroid glands resulting in hypoparathyroidism is the most commonly accepted reason, but nonspecific hemodilution associated with the stress of surgery is also involved. Some authors have suggested a release of thyrocalcitonin secondary to manipulations of the thyroid gland,[16-18] but this explanation has also been refuted by others.[5,19] Calcitonin administration to normal subjects even in large doses is not followed by hypocalcemia. In our series, serum thyrocalcitonin levels were measured serially in 36 patients. The mean H0 value was 2.2 ± 2.6 pg/mL, and mean values at the other times of blood withdrawal were even slightly lower (data not shown). We never found elevated levels of thyrocalcitonin at any time or for any patient. After subtotal thyroidectomy for hyperthyroidism, it has been suggested that mild hypocalcemia could result from sudden reversal of a negative bone and calcium balance (the so-called hungry bone phenomenon). However, this mechanism has been questioned, because almost all patients have been rendered euthyroid for many weeks preoperatively, and the osteodystrophy has largely been corrected before surgery. Anyway, this hypothetic explanation does not fully apply to our series, since only 13 patients had hyperthyroidism.

Falk et al,[5] measuring directly ultrafilterable calcium, found that after unilateral lobectomy, total calcium levels were significantly decreased postoperatively, whereas free calcium and PTH were not altered. They postulated a causative role of hemodilution, ascertained by a significant decrease in albumin level. Conversely, in their study, after total or subtotal thyroidectomy, albumin and both total and free calcium decreased significantly, whereas, rather curiously, neither PTH nor calcitonin serum levels were significantly altered, probably because of poor sensitivity of the assays. As the decrease in serum ionized calcium is the major stimulus of PTH secretion, these authors interpret their results showing simultaneous low levels of calcium and PTH as a temporary hypoparathyroidism. In 2 publications,[5,20] serum PTH concentrations are said to be lower in patients with postthyroidectomy hypocalcemia than in patients without hypocalcemia.

In our series, serum PTH, total calcium, and proteins dropped significantly early after surgery and remained at a low level until H96, whereas calculated ionized calcium remained unchanged compared with the preoperative value, which was in the lower part of the normal range (1.05 to 1.30 mmol/L). These findings strongly support a causative role of hemodilution. However, several of our experimental findings, other than the coexistence of simultaneous low levels of total and ionized calcium and PTH, suggest that a functional hypoparathyroidism was associated with hemodilution. The profiles of time evolution of PTH, total calcium, and proteins in the whole population were not strictly parallel, with proteins showing a significant decrease from H6 to H96, whereas total calcium reached its nadir at H24. The positive correlation between PTH and total calcium at times H48, H72, and H96 and between the nadirs of PTH and calcium in our overall population also favored a causative role of hypoparathyroidism, since in normal conditions these parameters are inversely correlated. Total calcium was significantly lower after total thyroidectomy than after hemithyroidectomy, whereas proteins did not differ significantly, thus indicating a similar amount of hemodilution.

Calculated (protein-adjusted) ionized calcium might not adequately reflect true ionized calcium concentrations during the postoperative period. It has been known for a long time that factors other than total proteins can alter the bioavailable (free or ionized) calcium; blood pH, albumin-globulin ratio, and magnesium concentration are the most prominent of these factors. Some of these parameters might be affected by surgery. It is therefore possible that under our conditions, the protein adjustment did not lead to an accurate assessment of ionized calcium. Direct determination of ultrafilterable calcium would have been preferable.

In conclusion, we believe, like other authors,[5,12] that the risk of permanent hypoparathyroidism after thyroid surgery had been previously overstated in the literature, probably because less attention was paid to the preservation of intact vascularity from the parathyroid arteries. On the contrary, temporary hypoparathyroidism after thyroid surgery is a frequent but benign condition and is not predictive of permanent hypocalcemia. Its pathogenesis should be better understood with the development of more sensitive PTH immunoradiometric assays.

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FUNCTIONAL SINUS TECHNIQUES

An international course on functional sinus techniques will be held in Graz, Austria, September 2-4, 1993. It will be conducted in English. For further information, contact Prof Dr Heinz Stammberger, University ENT-Hospital, Auenbruggerplatz 20, A-8036 Graz, Austria; telephone 43-316-385-3448; fax 43-316-385-3425.

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SAN FRANCISCO OTOLOGY, NEUROTOLOGY, & SKULL BASE SURGERY UPDATE — 1993

The San Francisco Otology, Neurotology, & Skull Base Surgery Update — 1993 will be held at the Ritz-Carlton Hotel, San Francisco, California, November 4-6, 1993. For further information, contact Office of Continuing Medical Education, Registration Office, Room LS-105, University of California, San Francisco, CA 94143-0742; (415) 476-5808.

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Ann Otol Rhinol Laryngol 102:1993

HIGH-SPEED, LIGHT-INTENSIFIED DIGITAL IMAGING OF VOCAL FOLD VIBRATIONS IN HIGH OPTICAL RESOLUTION VIA INDIRECT MICROLARYNGOSCOPY

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Digital imaging of vocal fold vibrations is mainly limited by lighting problems. We present a new technique for high optical resolution of vocal fold vibrations (via indirect microlaryngoscopy) using a light intensifier camera. Superficial epithelial structures and secretions can be followed during vibrations by means of high magnification. Recordings of up to 2.4 seconds and 6,000 frames per second, combined with simultaneous recording of acoustic and electroglottographic signals, are possible. This technique allows instant slow-motion monitor control and subsequent documentation on a normal video recording system. We also present preliminary findings of typical vocal fold motion patterns.

KEY WORDS — **high-speed digital video imaging, indirect microlaryngoscopy, light intensifier camera, vocal fold vibration.**

INTRODUCTION

High-speed imaging of vocal fold vibration (VFV) has been studied since the 1930s. At first, extensive effort was required to produce a short sequence of film because of lighting problems. Film development took at least a day. Analysis of single frames was time-consuming and troublesome.[1-10] In recent years, digital recording systems were introduced.[11-13] The availability of optical instruments such as flexible and rigid endoscopes in combination with convenient handling of computers opened a wide range of applications of VFV studies.[14,15] Recordings were confined to very short sequences, under 1 second, because of the technical limitations of computers and lighting problems when recordings reach high speed (up to several thousand frames per second).[11,13] Our interest has been aimed at high-resolution imaging of selected parts of the vocal fold in various modes of phonation, especially in situations in which stroboscopy cannot provide information about vibration characteristics, eg, aperiodic or aphonic vibration sequences.

METHODS

Laryngoscopy. For indirect microlaryngoscopy we used a standard microscope (Zeiss Germany, model Op-Mi 1-FC, objective lens f = 300 mm or 400 mm, magnification 0.6x to 2.5x). Camera adaptation was realized by an optical divider (Zeiss Germany). Real-time imaging control via the camera system and monitor allowed instant adjustment of picture details during examination with a microscope or flexible or rigid endoscopes.

Camera System. The Kodak EktaPro EM Motion Analysis system in combination with the Image Intensified Imager was used in this investigation. It consists of a camera, a control unit, and a memory unit. It involves a CCD image sensor, light intensity magnification 1,500x, and 48,000 pixels per image. There is variable adjustment of gain, gating, impulse time, and frame rate per second. Use of 1,000 frames per second resulted in full image display on the monitor; a higher speed restricted the display on the monitor to smaller bands proportional to the speed factor, while keeping high picture resolution in the remaining band. Scan selection on the monitor was horizontal, so we chose to display the vocal folds in the same orientation. Triggering was set retrograde (optionally anterograde) with a self-built, specially adapted generator (synchronizer). This marking permits later frame-by-frame comparison with other data such as acoustic and electroglottographic signals. The slow-motion playback function (forward and backward) of the camera system at frame rates from 1 to 1,000 frames per second allowed repeated visual analysis of the images immediately after recording. Sequences of interest were documented on videotapes (Sony, U-Matic format).

Phonation. Investigations of VFV patterns and characteristics were determined by protocol. Smooth, creaky, modal, and breathy voice intonations, as well

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Presented at the XXIInd World Congress of the International Association of Logopedics and Phoniatrics, Hannover, Germany, August 9-14, 1992.

REPRINTS — Markus M. Hess, MD, Dept of Audiology and Phoniatrics, Free University of Berlin, Steglitz Medical Center, Hindenburgdamm 30, 1000 Berlin 45, Germany.

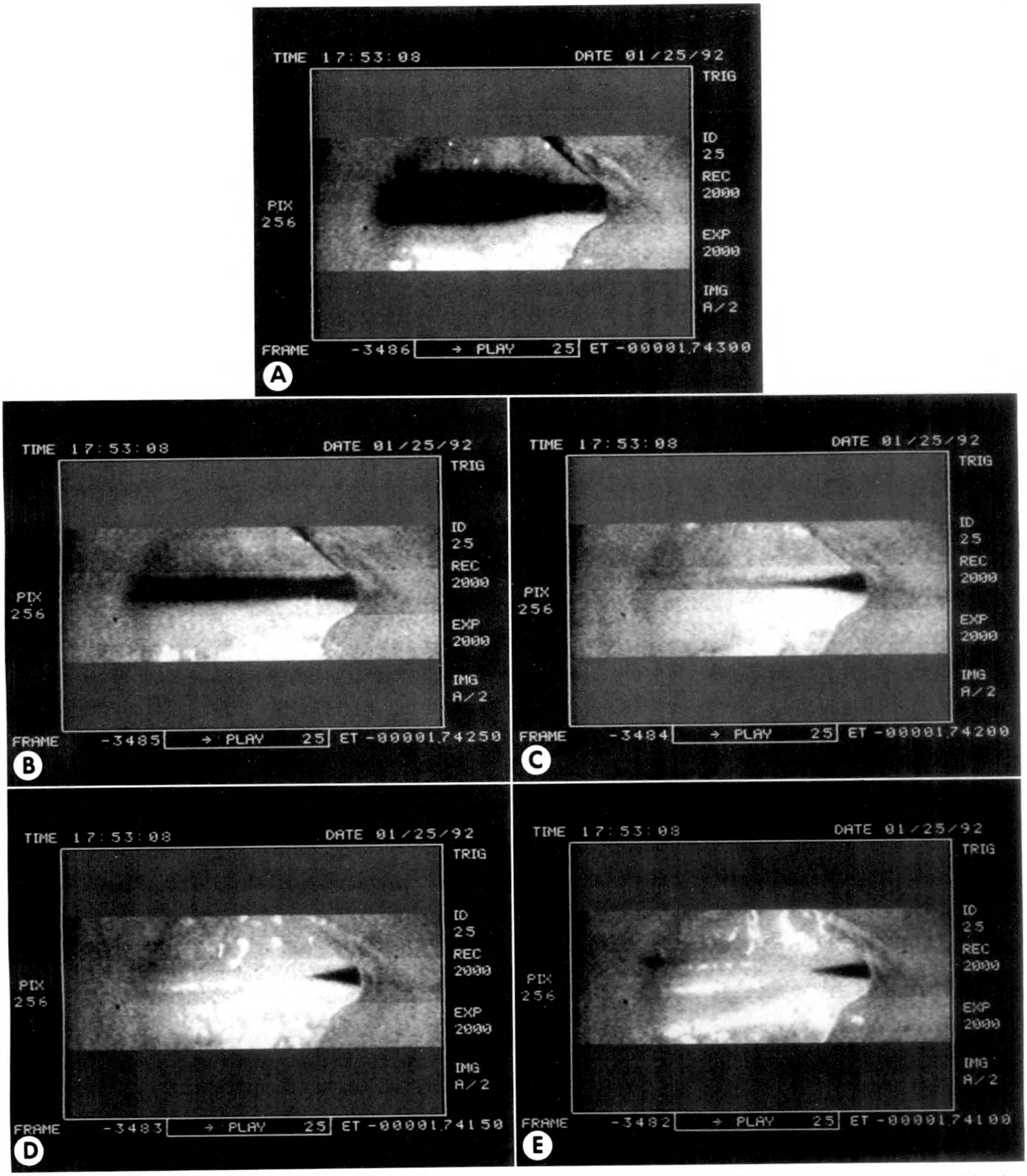
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Fig 1. A-I) One cycle (consecutive images) of vocal fold vibration in larynx of female subject. Display of habitual pitch and habitual loudness. Anterior commissure is on left side of picture. Left bottom corner of each picture shows chronologic count (from – to +). Right corner shows time in seconds. There is good optical resolution of vocal folds; details can be observed; frame identification is convenient. REC — 2,000 frames per second; → PLAY — playback mode forward with 25 frames per second. (Continued on next page.)

as glissando and swelling tones (crescendo-decrescendo), at different pitch and sound pressure levels were recorded. Vibration of the epiglottis and aryepiglottic region in singing of tremolo and vibrato could also be seen with the rigid endoscope.

RESULTS

Typical pictures of high-speed imaging at 2,000 frames per second are seen in Figures 1 and 2. The vocal folds are displayed horizontally. Details of the vocal fold surface can be identified. Lighting was

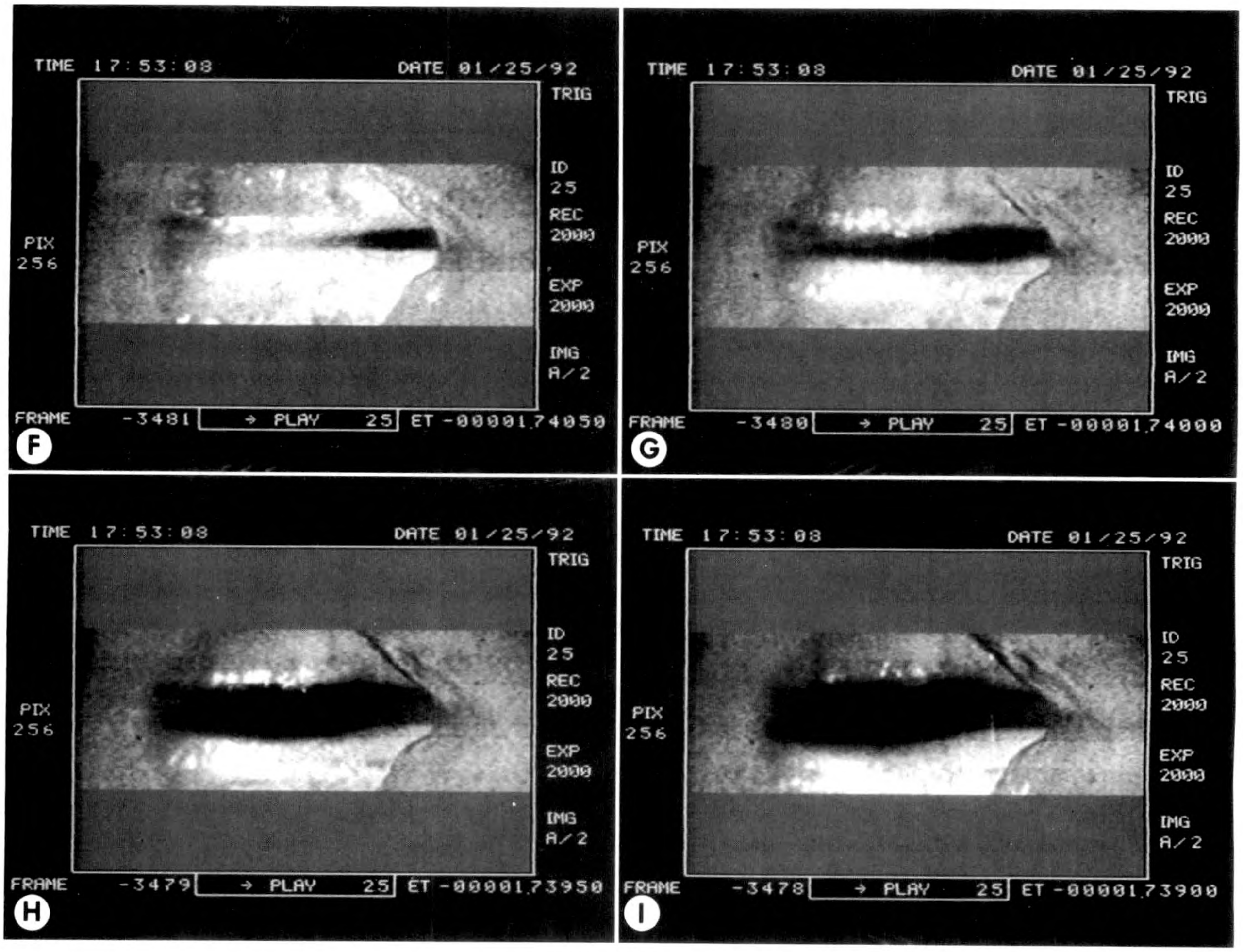

Fig 1, continued.

sufficient when recording parameters were set at an amplification of 50%. The depth of focus was sufficient for the true vocal fold surface and parts of the false vocal folds and the arytenoid region. Time periods of 2.4 seconds were long enough for registration of most phonations (Fig 1).

The adaptation of the rigid endoscope to the camera and mirror technique for visualization of the vocal folds in indirect microlaryngoscopy requires some practice. We were impressed by the feasibility of slow-motion playback of the pictures stored in the random access memory before final rerecording onto a videotape. This facilitated the decision whether or not to repeat the examination.

Figure 2 shows the vocal folds coming into contact at initiation of phonation. The pictures are compared to the electroglottogram (middle) and acoustic signal (lower part of Figure; not corrected for time delay of 2 milliseconds).

DISCUSSION

Light-intensified digital imaging in combination with indirect microlaryngoscopy can provide good picture quality at high speed and with high optical resolution. Frame rates up to 6,000/s and periods of 2.4 seconds were sufficient for recording of most phonation types. Details of the vocal folds were demonstrated with indirect microlaryngoscopy without an additional light source (and so without unpleasant warming of the mucosa). A broad spectrum of investigational variability was offered by different examination types (indirect microlaryngoscopy, flexible or rigid endoscopy). Although kymography allows visualization of VFV patterns in a restricted form, the light-intensified imaging technique permits a better investigational setting for examination of aperiodic and aphonic sequences of different phonation types.[16,17] These aperiodic phonations cannot be visualized satisfactorily with laryngostroboscopy because of triggering conditions.

A great advantage was given in the immediate control of picture adjustments via real-time display on the monitor and by recording control with slow-motion playback at various speeds forward and backward.

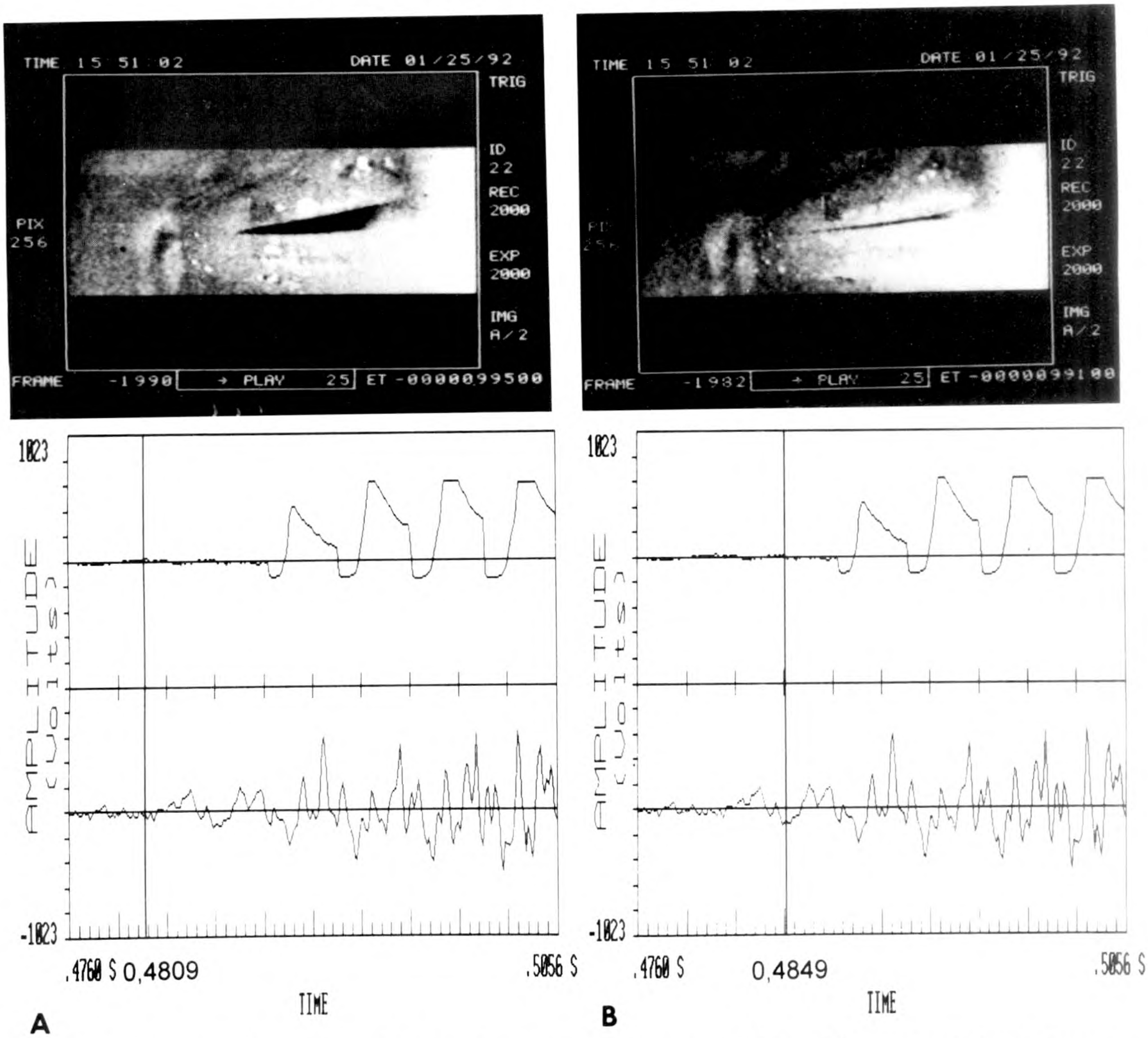

Fig 2. A) Abducted site of vocal folds. No signal in electroglottogram (EGG; middle portion of figure). Lowest trace is acoustic signal. B) One cycle before first contact: vocal folds almost contact each other. No signal in EGG. First acoustic signals are seen (lower signal in figure; not corrected for time delay of 2 milliseconds). (Continued on next page.)

Sampling of high frame rates resulted in narrowing of the displayed band on the monitor. Fortunately, during phonation the vocal folds could be seen completely when arranged horizontally on the monitor. By varying the magnification on the microscope, different aspects of the endolarynx were visualized.

Reflection patterns of the lubricated vocal fold surface contributed to the plasticity of imaging. These reflections facilitated analysis of surface motion and VFV patterns. We also marked the surface of the vocal folds with a special preparation of a nontoxic adhesive paste that allowed examination of distinct areas of the epithelium. Further studies of pattern variability under different mass volumes are in preparation.

One of the most interesting phenomena was initiation and stabilization of VFV.[18-20] With a breathy voice this period was longer than with a modal voice. Changes to other registers can distinctly be seen and determined in slow-motion playback. Lengthening of the vocal folds and reduction of the epithelial movements in glissando can also be seen with indirect microlaryngoscopy. The position of the epiglottis in glissando and swelling tones, as well as in vibrato and tremolo singing, was visualized with rigid endoscopic imaging. Periodic swinging of the epiglottis and of the mucosa in the endolarynx and hypopharynx could be observed. In vibrato singing, the vocal folds periodically lessen their amplitudes, depending on the anterior-posterior position of the epiglottis. Comparisons with acoustic and electroglottographic signals have been undertaken and will be published later.

Another advantage of indirect microlaryngoscopy is the possibility of measuring objects that are in focus. In this case we could exactly measure amplitudes and, in specific cases, the length of marked

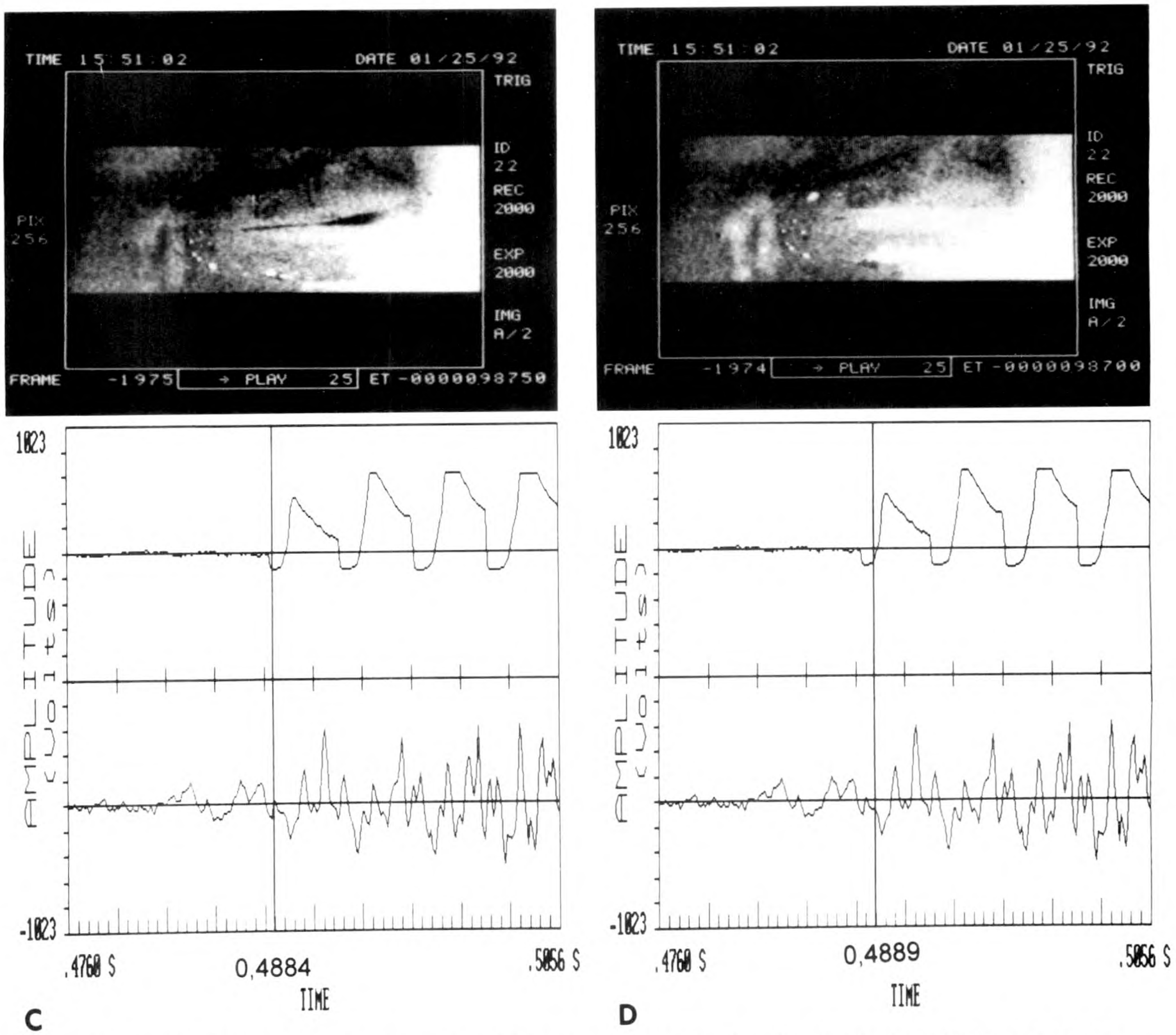

Fig 2, continued. C,D) Ventral parts of vocal folds come into contact first. Note beginning of EGG signal in this phase. Little discrepancy is seen between closed folds and EGG signal, which becomes positive just afterward (perhaps because of inaccuracy of synchronization of camera and signal recorder).

areas on the surface of the vocal folds.

We assume that the terminology of different phonation types might be more easily clarified with digital imaging as in this setting.[21] Because of high initial costs of the camera system (in Germany the camera system costs about US $250,000), the use of light-intensified imaging will be confined to a limited number of investigators. A combination of indirect microlaryngoscopy with stroboscopy and light-intensified imaging (eg, selectable by foot switch) might be practicable when examining a patient, eg, before and after an operation under local anesthesia.

ACKNOWLEDGMENTS — The authors thank Uwe Schönfeld, Dipl Ing, for his assistance in preparing the synchronizer and for technical assistance, and Jan Jacobs (Kodak Company, Stuttgart) for advice on technical methods of imaging with the camera system.

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THIRD INTERNATIONAL SYMPOSIUM ON MENIERE'S DISEASE

The Third International Symposium on Meniere's Disease will be held October 20-23, 1993, in Rome, Italy. For information, contact Kugler Publications bv, Congress Department, PO Box 1498, New York, NY 10009-9998; telephone (212) 477-1970; fax (212) 477-0181.

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SIXTH INTERNATIONAL CONGRESS ON INTERVENTIONAL ULTRASOUND

The Sixth International Congress on Interventional Ultrasound will be held September 7-10, 1993, in Copenhagen, Denmark. For information, contact Christian Nolsøe, Congress Secretary, Department of Ultrasound, Herlev Hospital, University of Copenhagen, DK-2730 Herlev, Denmark.

Ann Otol Rhinol Laryngol 102:1993

POSTURAL CONTROL IN YOUNG AND ELDERLY ADULTS WHEN STANCE IS CHALLENGED: CLINICAL VERSUS LABORATORY MEASUREMENTS

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ALBERT SCHULTZ, PHD
MIAN JU GU, PHD

NEIL B. ALEXANDER, MD
THOMAS BOISMIER, MPH

ANN ARBOR, MICHIGAN

The use of dynamic posturography (EquiTest) for the characterization of postural control biomechanics would be aided by specific knowledge of what the measured data imply about body segment movements. To investigate this issue, the biomechanics of a group of 15 healthy elderly subjects were compared to those of healthy young subjects by using both dynamic posturography and a laboratory movement and force measuring system. The results from EquiTest were analyzed by 1) routine clinical interpretation of data and 2) a clinical research interpretation by subjecting the EquiTest parameters to additional statistical comparison of mean performance of the young and elderly groups. The young-elderly differences from the 2 EquiTest analyses were then compared to the young-elderly differences derived from the laboratory protocol. The routine clinical interpretation of EquiTest data identified the same increases in sway shown by the laboratory study, but did not reveal the more subtle differences indicated by the laboratory study. When the EquiTest data were subjected to additional statistical analysis, the characterization of difference between young and elderly subjects was the same as that of the laboratory study, with the exception of issues of head versus trunk movement, a measure not made by EquiTest. This essential similarity in the characterization of elderly compared to young subjects by both systems suggests 1) that EquiTest is able to detect subtle differences in biomechanics of postural control between young and elderly healthy adult groups and 2) that implied movements of center of gravity, trunk versus lower limbs, and strength of reaction measures are consistently detected by both EquiTest and the laboratory kinematics and dynamics measurement systems.

KEY WORDS — balance disorders, elderly, postural control.

INTRODUCTION

Characterizing postural control biomechanics is important when assessing patients with balance disorders, especially those who repeatedly fall. Dynamic posturography (EquiTest) is becoming more widely used as a clinical tool to describe sensorimotor and postural control biomechanics.[1-4] Dynamic posturography is also used as a research tool to characterize the developmental aspects of postural control, the biomechanics of static and dynamic stance under various environmental conditions, and the pathophysiology of specific clinical entities.[5-9] Because dynamic posturography is applied both clinically and as a research tool in a variable manner, knowing what information it provides is important.

EquiTest uses force plate data to calculate estimates of center of mass (center of gravity [COG]) movements to infer relative body segment motions. In order to have an evaluation tool that is both clinically practical and accurate, dynamic posturography acquires data only on vertical and horizontal support surface reaction forces. Although myoelectrical recordings are used in research settings, they are not presently used in standard clinical tests. Aspects of the biomechanics of postural control might be missed or erroneously interpreted, since interpretation of the reaction force data assumes that the body functions as an inverted pendulum system.

The purpose of this study was to compare biomechanical results from clinical dynamic posturography (EquiTest) to a research laboratory kinematic and dynamic analysis of responses to postural disturbances in healthy elderly and healthy young adult subjects. We hypothesized that the characterizations of postural control would not differ between the clinical and the research data collection systems when either 1) dynamic posturography was analyzed in a typical clinical fashion or 2) a more detailed statistical analysis of the dynamic posturography data was performed.

METHODS

Subjects and Comparisons. The EquiTest perfor-

From the Department of Otolaryngology (Shepard, Boismier), the Department of Mechanical Engineering and Applied Mechanics (Schultz, Gu), and the Division of Geriatric Medicine, Department of Internal Medicine (Alexander), University of Michigan, and the Geriatric Research Education and Clinical Center, Ann Arbor Veterans Administration Medical Center (Alexander), Ann Arbor, Michigan. Supported by the Vestibular Testing Center of the Department of Otolaryngology, Public Health Service grants AG06621 and AG08808, the Dana Foundation, the Vennema Endowment, and the Turner Geriatric Clinic.

REPRINTS — Neil T. Shepard, PhD, Vestibular Testing Center, Rm C166A, Med-Inn Bldg, 1500 E Medical Center Dr, Ann Arbor, MI 48109-0816.

TABLE 1. MOVEMENT COORDINATION PLATFORM MOVEMENT PROTOCOL

Perturbation Type	*Size*	*No.*
Backward translation	Small	3
	Medium	3
	Large	3
Forward translation	Small	3
	Medium	3
	Large	3

mance of 15 healthy elderly volunteers, 8 women and 7 men (mean age 72.3, range 66 to 79 years), was compared to normative data provided by NeuroCom International, Inc, for EquiTest over the age range 20 to 59 years. The research laboratory study[10,11] compared responses of the 15 elderly volunteers to those of a group of 12 female and 12 male healthy young adults (mean age 25, range 18 to 33 years). The elderly subjects were evaluated first in the research laboratory and then with dynamic posturography, during a single 4-hour session.

A detailed medical history was obtained and a physical examination that focused on musculoskeletal and neurologic items was conducted by a physician geriatrician in all elderly subjects. All subjects denied histories of significant head trauma, otologic or neurologic disease, visual impairments not correctable with lenses, limb or spinal fracture, or persistent symptoms of vertigo, lightheadedness, or unsteadiness. Some elderly subjects, although denying significant impairment, had subtle abnormalities on history and physical examination. The details of these findings are given by Alexander et al.[10] Despite these minor abnormal findings on history and examination, all elderly subjects were physically active in either regular exercise or walking programs. They represented a relatively healthy group that lived independently.

Dynamic Posturography (EquiTest) Study. The method for performing clinical dynamic posturography and its clinical utility are described elsewhere,[4,12,13] but present purposes warrant detailed review of this method. Each of the elderly subjects was placed on the dual force plate platform of the EquiTest equipment and secured with a harness to prevent a fall. The 2 portions of dynamic posturography, movement coordination (MC) and sensory organization (SO), were then conducted in a clinically routine manner without a rest period, with software version 3.02.

Movement coordination tests[4] involve sudden posterior and anterior translations of the patient's support surface (Table 1). Center of support surface reaction force (COF) excursions, derived from the force plate data, are used to estimate center of mass (alternatively, COG) movements (see Appendix). The amplitude and duration of excursions for each translation magnitude are normalized by subject height to produce an assumed equivalent COG sway angle (Table 2). The maximum velocity for a given translation is 15.24 cm/s (6 in/s), with time to maximum velocity 50 milliseconds. This implies an approximate acceleration of 304.8 cm/s^2.

TABLE 2. MOVEMENT COORDINATION PLATFORM MOVEMENT SPECIFICATIONS

Perturbation	*Duration (ms)*	*Amplitude*	*Equivalent Sway*
Small translations	250	$0.5 \times \frac{\text{Height}}{72}$ in	0.7°
Medium translations	300	$1.25 \times \frac{\text{Height}}{72}$ in	1.8°
Large translations	400	$2.25 \times \frac{\text{Height}}{72}$ in	3.2°
Rotations	400	8°	8°

Sensory organization tests evaluate 6 test conditions (Fig 1) that systemically vary the visual and foot somatosensory cues available to the subjects while they attempt to maintain stable, quiet stance. No manipulation of vestibular end organ inputs is attempted. Condition 1 had 1 trial, condition 2 had 2 trials, and conditions 3 through 6 had 3 trials each. Each trial was performed for 20 seconds. Conflicting sensory inputs are achieved by synchronizing patient COG movement to available visual and somatosensory cues (Fig 1). Visual stabilization synchronizes COG movement in the sagittal plane with the subject's visual surround. Somatosensory stabilization tilts the support surface about an axis parallel to the axis through the ankle joints.

Analyses of the changes in vertical floor reaction forces for both MC and SO are used to calculate the COF excursion. From the COF an estimated COG movement is derived that is then used to calculate an equilibrium score for an estimate of sagittal plane sway for the 6 SO conditions (see Appendix). As the magnitude of the COG excursion increases, the equilibrium score decreases. For MC the COF is measured separately for each foot and is used directly for calculating latencies to onset of active COF response to horizontal translations and response strengths. The COG is calculated from COF for the platform translations and plotted, but is not used to determine any response parameters for MC testing.

For the purposes of this report, "routine clinical use" of EquiTest relates to the comparison of individual and group elderly performance against the clinically established threshold for normal versus

SENSORY ORGANIZATION PROTOCOL

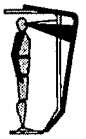
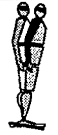
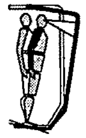
Condition	Vision	Support	Patient Instructions
1	Normal	Fixed	Stand quietly with your eyes OPEN
2	Absent	Fixed	Stand quietly with your eyes CLOSED
3 	SwayRef	Fixed	Stand quietly with your eyes OPEN
4	Normal	SwayRef	Stand quietly with your eyes OPEN
5 	Absent	SwayRef	Stand quietly with your eyes CLOSED
6 	SwayRef	SwayRef	Stand quietly with your eyes OPEN

Fig 1. Shown are 6 test conditions for sensory organization portion of dynamic posturography. In first 3 conditions, accurate foot somatosensory cues are available to patient in all tests. First and second conditions are simply eyes-open and eyes-closed Romberg tests, performed 1 to 2 times each with 20-second trial. Condition 3 provides for inaccurate visual orientation information (visual conflict), in that if patient sways anterior or posterior, visual surround moves with patient. In conditions 4, 5, and 6, inaccurate foot somatosensory cues are provided by tilting platform by amount equal to patient's anterior-posterior sway. Then, for each of these conditions (4, 5, and 6), same visual variations are tested as in conditions 1, 2, and 3. Therefore, in conditions 5 and 6, only accurate input cue is vestibular end organ information. In conditions 3 through 6, three 20-second trials of each are performed. (Figure developed by and permission for use provided by NeuroCom International, Inc.)

abnormal performances in a 20- to 59-year-old normative group. Abnormal performance is defined as scores for an individual (or mean scores for the elderly group) that are lower than the fifth percentile performance range for the 20- to 59-year-old normals for SO, or outside a 2 SD range of the 20- to 59-year-old group mean performance for MC.

The "research use" of EquiTest relates to the direct additional statistical comparison of the mean performance for statistically [illegible] differences of the 20- to 59-year-old group [illegible] elderly group on all measures of performance [illegible] by the standard EquiTest protocol for [illegible] significant differences in mean performance [illegible] accepted at the p ≤ .05 level evaluated by Student's t test. For this analysis the elderly [illegible] scores, SO strategy scores, latencies [illegible]ions, strategy scores for translations and [illegible] strengths for translations were [illegible] the young group mean scores for [illegible] parameters by using Student's *t* test [illegible] statistically significant differences. [illegible] to the "routine clinical" analysis, in which [illegible] individual or elderly group mean scores on the same parameters were compared to limits of normal clinical performance for the young group. The limits of normal represent a less rigorous, general comparison for statistically significant differences between the 2 groups.

Analyses of MC tests [illegible] response latency and response strength for each leg. Latency is defined as the time following translation onset when the subject begins to actively resist the induced sway. This time is calculated from COF anteroposterior movement. The COF excursion data are differentiated, and the time at which the rate of change in COF excursion exceeds a threshold value [illegible] (see Appendix). Response strength is defined as the time rate of change in the support surface COF (slope of the COF excursion trace) during [illegible]second interval following the onset latency (see Appendix). The MC output measures of weight distribution and adaptation were not used in this study.

For both SO and MC the sum of left and right foot anteroposterior shear force was measured by a force transducer in the force plate support system. A movement strategy score was derived from the shear force measures such that an increase in shear force resulted in a decrease in the movement strategy score (see Appendix). The movement strategy score was calculated for each trial of each SO test, and for each posterior and anterior translation test during MC. When more than 1 equilibrium or movement strategy score was available for a given task, an average of those scores was used to represent that performance. The latency to onset and response strength measures for each leg were respectively averaged to produce a single latency and single strength output for each of the MC conditions.

Laboratory Study. Alexander et al[10] and Gu et al[11] have described in detail the methods used to assess the kinematics and dynamics of postural disturbance responses in the 15 elderly and 24 young adults.

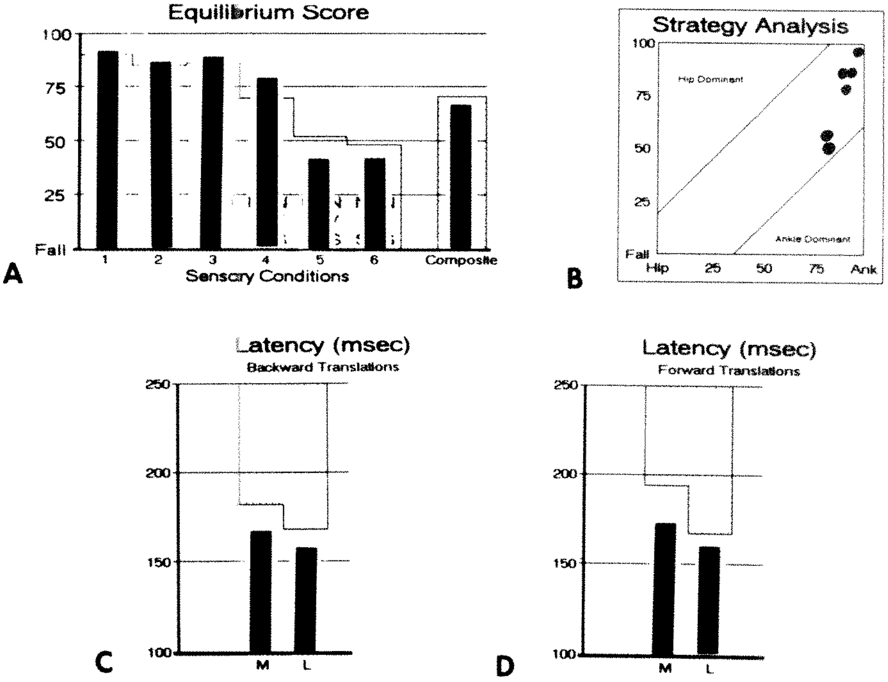


Fig 2. Mean performance of elderly group presented against clinical range for 20- to 59-year-old normal subjects. A) Results on each of 6 sensory organization conditions. Equilibrium score is percentage, with 100% indicating no sway and "fall" indicating magnitude of sway equal to theoretic limit of stability (see Appendix). Composite bar graph is mathematic average of 6 test condition results. Stippled area represents abnormal performance (fourth or lower percentile range) compared to 20- to 59-year-old normal group. Bars indicate mean performance of 15 elderly subjects. Only conditions 5 and 6 show performance in abnormal range, indicating increased magnitude of center of gravity sway compared to young subjects on these 2 conditions. Composite score is abnormal because of below-normal performance on conditions 5 and 6. B) Plot of movement strategy score (abscissa) against equilibrium score (ordinate) for each of 6 sensory organization conditions tested. Data points indicate mean performance of 15 elderly subjects for each of 6 tested conditions. Clinically, movement strategy score is viewed relative to amount of sway. C,D) Group mean latency to onset of active center of support surface reaction force response to posterior perturbations of medium and large size and to anterior perturbations of medium and large size, respectively, for 15 elderly subjects. Latencies are given in milliseconds, with stippled area representing latencies having values at or greater than 2 SD above mean latency for 20- to 59-year-old normals.

Those methods will be reviewed only briefly here.

Each subject stood upright with feet bare, eyes closed, and hands clasped in front of the abdomen on a force plate. The force plate, mounted on a computer-controlled moving platform, measured support surface reactions. The rotations of all major body segments were measured with an optoelectronic camera system (Watsmart) and 11 light-emitting diodes attached to the right side of the body. Subject responses were tested in 4 tasks.

1. Flat translation. The force plate was accelerated in random anterior or posterior directions, followed by constant velocity and deceleration phases. Only responses to anterior accelerations were analyzed.
2. Beam standing. The subject stood for 10 seconds on a stationary 11-cm-wide beam attached to the force plate.
3. Beam translation. The subject stood on the 11-cm-wide beam while it was accelerated in random anterior or posterior directions, followed by constant velocity and deceleration phases. Only responses to anterior accelerations were analyzed.
4. Springboard standing. The subject stood 10 seconds on a torsional spring–loaded platform that would rotate about an axis parallel to the ankle axis 0.8° for each degree of sagittal plane body tilt.

In both translation tasks the acceleration, constant velocity, and deceleration phases all lasted 100 milliseconds. The constant velocity achieved was 16.3 cm/s in flat translation and 9 cm/s in beam translation.

The protocol for these laboratory tests was designed to disturb the postural control system with non–fall-producing conditions. The protocol was not designed to replicate EquiTest conditions. However, the springboard standing and flat translation tasks were similar to EquiTest SO condition 5 (SO5) and the MC large translation tasks, respectively.

The COF and COG excursions, angular momenta, and joint torques were derived from a combination of

TABLE 3. SENSORY ORGANIZATION EQUILIBRIUM SCORE

SO Condition	*20-59 Years* (N = 112)*	*66-79 Years (N = 15)*	*p*
SO1	94 ± 2.4	92 ± 3.6	<.05
SO2	92 ± 4.2	87 ± 8.1	NS
SO3	91 ± 3.4	86 ± 4.3	<.001
SO4	82 ± 7.6	78 ± 9.3	NS
SO5	69 ± 10.4	37 ± 15.1	<.001
SO6	66 ± 12.3	39 ± 15.5	<.001

Data are mean ± 1 SD.

SO — sensory organization, NS — not significant.

*On this and other Tables, data for ages 20 to 59 years are normative data provided by NeuroCom International, Inc.

measurements and biochemical model computations. The COG location was computed by using the measured individual body segment motions and anthropometric data scaled to each subject's height and weight. The torques developed at all major body joints were computed by using the measured body segment motion data, the anthropometric data, and a 7-link biomechanical model of the body.

Onset latency for the COF movement to actively resist the induced backward sway (anterior platform translation) was calculated by computer and defined as the time after platform translation onset when the COF rate of change exceeded 10% of its 2-second averaged predisturbance magnitude for that individual subject. Therefore, for both the latency to onset of an individual body segment and for the COF active movement, the individual's baseline activity prior to translation (2 seconds) served to set the threshold point that had to be exceeded by 10% to be considered active resistance to the induced backward sway. This is in contrast to the latency to onset of COF movement from MC of EquiTest, in which an absolute threshold for determining onset of COF active movement was used.

RESULTS

Laboratory Study. The detailed results from the research laboratory comparison of elderly versus young adults have been presented by Alexander et al[10] and Gu et al.[11] A brief summary of the findings is given below.

Compared to young adults, healthy elderly subjects with no apparent musculoskeletal or neurologic impairment had small but significant differences in postural control response biomechanics, but the order of magnitude of these differences was condition-specific. The differences were especially notable in the beam standing and beam translation tasks.

All subjects responded with segment rotations that were small. The elderly rotated the head, trunk, and arms more than the young, primarily in the 2 beam tasks. Consistent with these kinematic findings, the elderly developed larger joint torques, most pronounced at the hip joint, and greater anteroposterior shear forces than the young, with both of these age group differences significant in the 2 beam tasks.

TABLE 4. SENSORY ORGANIZATION MOVEMENT STRATEGY SCORE

Strategy Condition	*20-59 Years (N = 112)*	*66-79 Years (N = 15)*	*p*
ST1	98 ± 1.5	97 ± 2.3	NS
ST2	98 ± 1.4	94 ± 2.4	<.001
ST3	96 ± 5.8	93 ± 2.8	<.01
ST4	88 ± 2.0	91 ± 2.8	<.001
ST5	82 ± 6.6	76 ± 6.8	<.001
ST6	83 ± 6.0	77 ± 7.9	<.001

Data are mean ± 1 SD.

ST — strategy, NS — not significant.

In response to both anterior acceleration tasks, except for the head, initial body segment rotations were counterclockwise as viewed from the right side. The primarily clockwise initial head rotation direction suggested an attempt at head stabilization with respect to the vertical rather than to the body. That head rotation was highly variable in the elderly, especially in beam translation, suggested increased difficulty with head stabilization. Body segment rotations in both translation tasks began in the shank, were followed by the thigh, and then moved proximally to the remaining segments, with no significant age group differences. The head tended to be rotated before the trunk and arms in the beam translation task in both groups, with no young-elderly differences. Latency to onset of active COF movement (passive movement is instantaneous) was significantly longer ($p < .01$) in the young (mean 119 milliseconds, SD 37.8 milliseconds) than in the elderly (mean 98.7 milliseconds, SD 17.9 milliseconds).

The excursions of the COG and the COF tended to be larger in the elderly than in the young, with the differences significant in the beam standing task. The frequency of oscillations in these excursions was also higher in the elderly than in the young. Angular momenta tended to be greater for the elderly than for the young during both translation tasks, with differences of statistical significance in the beam translation task.

Dynamic Posturography Clinical Use Findings. An SO equilibrium score was considered abnormal if it fell below the fifth percentile of performance range for the 20- to 59-year-old normals. Only SO conditions 5 and 6 showed clinically recognizable age group differences, with increased magnitude of COG sway in the elderly resulting in a group mean equilib-

TABLE 5. LATENCY TO ONSET OF ACTIVE REACTION TO TRANSLATION

Perturbation Type	*20-59 Years (N = 85)*	*66-79 Years (N = 15)*	*p*
Posterior medium	151 ± 13.7	168 ± 15.9	<.001
Posterior large	139 ± 14.0	168 ± 16.0	<.001
Anterior medium	153 ± 20.0	171 ± 22.0	<.01
Anterior large	138 ± 14.0	161 ± 21.0	<.001

Data are mean ± 1 SD.

rium score in the abnormal range for 20- to 59-year-old normals (Fig 2A).

When the elderly were compared individually instead of as a group, 73% (11 of 15) were abnormal in SO5 and SO6. In the other SO tests the number of abnormal performances ranged from 0% in SO4 to 33% (5 of 15) in SO2. Clinically, a single fall reaction during any test, but especially during SO5 or SO6 with the remainder of conditions normal, is not considered abnormal. As a group, the elderly showed a mean of 0.5 and 0.4 falls, respectively, in SO5 and SO6, with no falls in any other SO test. Individually, 6 subjects had a single fall reaction in SO5, and 5 a single fall reaction in SO6. One subject had 2 fall reactions in SO5, and another subject had 2 fall reactions in SO6; both of these subjects were over 70 years of age.

A movement strategy score was considered abnormal when it was greater than 2 SD below the mean score for the 20- to 59-year-old group. When movement strategy during SO testing (a potential indicator of upper body movement because a decrease in movement strategy score reflects an increase in horizontal shear force) was normalized by the magnitude of COG sway (equilibrium score) in the sagittal plane (Fig 2B), the elderly as a group and individually showed no indications of clinically abnormal movement strategy. Discussed below, additional statistical analysis of the strategy scores (not normalized for sway magnitude) by Student's *t* test comparing the mean elderly and young groups showed a statistically significant decrease in score for the older group (see Dynamic Posturography Research Use Findings).

During MC a latency to onset of active COF response to induced forward or backward sway was considered abnormal if it was more than 2 SD above the mean for 20- to 59-year-old normals. No clinically significant age group differences in mean latency to active onset of reaction to anterior or posterior surface translations were noted. However, 27% (4 of 15) of the elderly subjects had latencies that were individually clinically abnormal, in response to both medium and large perturbations in either the anterior or posterior directions, compared to the 20- to 59-year-olds' normative data. As with the strategy score data, when the mean elderly group latencies were subjected to additional statistical comparison with the young group latencies via Student's *t* test, group differences were realized (see Dynamic Posturography Research Use Findings).

Dynamic Posturography Research Use Findings. Differences in mean values between the 15 elderly subjects and the 20- to 59-year-old normative population were significant for a large number of the EquiTest performance parameters studied. The major exceptions to this were the movement strategy scores and the response strength (rate of change of COF) measures during MC (Tables 3-7).

The elderly showed greater magnitude of COG movements than the normative group, with the differences significant for test conditions SO3, SO5, and SO6 (Table 3).

For the SO movement strategy scores (a measure of shear force), age group differences were generally significant. The elderly developed lower movement strategy scores (larger shear forces) than the normative group in all SO conditions except SO1 and SO4 (Table 4). The difference was not significant in SO1; the young developed a significantly smaller mean movement strategy score than the elderly in SO4.

The elderly showed significantly longer group mean latencies to onset of active response in the MC translations for all 4 conditions (medium and large translations for both anterior and posterior directions) compared to the mean latencies for the 20- to 59-year-old normals (Table 5).

No significant differences were seen between the mean movement strategy scores during MC for the elderly compared to the young (Table 6), with only 1 of the 4 response strength measures in the MC translation conditions showing a significantly different mean between the young and elderly (Table 7).

DISCUSSION

No previous comparison of healthy elderly to healthy young using dynamic posturography in the routine clinical analysis manner has been reported in the literature. However, our results on EquiTest are in agreement with reported healthy young compared to elderly performance when analyzed in the research manner defined in this paper. In work by Ledin et al[7] a group of 15 healthy individuals between 70 and 75 years old were evaluated on EquiTest using the standard clinical protocol for SO. Their mean equilibrium scores were then compared to those of the 20- to 59-year-old normals, just as done here. They reported statistically significant differences ($p < .001$),

TABLE 6. MOVEMENT STRATEGY SCORES FOR TRANSLATIONS

Perturbation Type	*20-59 Years (N = 85)*	*66-79 Years (N = 15)*	*p*
Posterior medium ST	82 ± 7.0	76 ± 11.5	<.001
Posterior large ST	75 ± 13.0	71 ± 15.0	NS
Anterior medium ST	75 ± 10.0	73 ± 15.0	NS
Anterior large ST	66 ± 13.0	68 ± 13.0	NS

Data are mean ± 1 SD.

ST — strategy, NS — not significant.

with the elderly showing lower equilibrium scores on SO2, SO3, SO5, and SO6. Our results also indicated significant differences at the $p < .001$ level for SO3, SO5, and SO6, with no difference on SO4. However, we found no difference on SO2, and a minor significant difference ($p < .05$) on SO1. In general, the agreement was excellent. Ledin et al[7] did not report a comparison of MC results with their elderly.

Findings from the present study are also in good agreement with recent studies by Peterka and Black,[14,15] who studied the effects of aging on performance in dynamic posturography with protocols similar to those used in this work, but not with EquiTest equipment. In evaluating individuals from 7 to 81 years of age, a slight trend for increased sway in the sagittal plane above age 60 was noted for SO4 and SO5, and a dynamic increase on SO6. Peterka and Black[15] report that for anterior and posterior platform translations, no age-related change in latency to onset of COF response was seen, but a slight increase in time to develop maximum ankle torque was seen with aging. No age effect on the magnitude of the torque was noted by these investigators.

Young-elderly differences characterized by routine clinical analysis of the EquiTest results suggest a trend for increased sway of the COG on the SO conditions (as reflected in lower mean equilibrium scores), and it is clinically significant only in SO5 and SO6. These findings of increased COG excursion in the elderly compared to the young with task-specific magnitude differences are the same as 1 of the age group difference findings from the laboratory study. However, the clinical analysis of the EquiTest data showed no other differences in the elderly as a group compared to the 20- to 59-year-old normals. This suggests that while sensitive on a task-specific basis to performance differences between the 2 normal groups, routine clinical analysis missed many of the more subtle differences characterized by the laboratory study.

When the EquiTest data were subjected to additional statistical analysis in the research manner, they suggested small but significant young-elderly differences in a number of biomechanical features, with the magnitude of the differences task-specific. It is of importance that the same general biomechanical differences were provoked by the laboratory and EquiTest studies under seemingly different test conditions. The beam standing and beam translation tasks from the laboratory study and the sway-referenced platform and sway-referenced visual surround conditions from SO of EquiTest evoked the greatest and most varied young-elderly differences. The only disagreement in young-elderly characterizations between the EquiTest and the laboratory studies related to latency to onset of active COF response to flat-surface anterior translations.

Both EquiTest, when analyzed in a research manner, from SO3, SO5, and SO6 and the laboratory beam standing condition showed significantly greater whole-body COG excursions in the elderly than in the young. In addition, the laboratory study showed that the frequency of oscillation of COF excursion was an important measure to demonstrate young-elderly differences. Significantly greater frequency of oscillation was noted for all 4 tasks studied for the elderly compared to the young. EquiTest does not directly address the issue of frequency of oscillation of COF, but does provide the calculated COG excursion trace for each of the 20-second SO trials and for the 2.5-second anterior and posterior translations. Therefore, at least an estimate of changes in oscillation frequency for COG can be developed. Note that COG movement may be modeled as a low-pass-filtered output of COF.[16] Therefore, estimates of sway oscillation frequency from COG may not have the same sensitivity as the direct COF measurements from the laboratory study.

EquiTest analyzed in the routine clinical or research manner does not have provision for measuring the movement of individual body segments. However, the movement strategy score is interpreted to imply information about the magnitude of trunk versus lower limb movements. Specifically, decreases in movement strategy score (shear force increases) suggest that greater movement of the upper body (predominantly the trunk) is occurring. When our EquiTest data were analyzed in the research manner, the movement strategy scores from SO2, SO3, SO5, and SO6 were significantly lower for the elderly than for the young. This suggests greater upper body movement in the elderly in response to these specific conditions. This same result was directly observed in the laboratory study. The elderly tended to use greater upper body compared to lower limb movement than the young in all conditions, with the difference significant in the 2 beam tasks. This was further indi-

TABLE 7. RESPONSE STRENGTH FOR TRANSLATIONS

Perturbation Type	*20-59 Years (N = 85)*	*66-79 Years (N = 15)*	*p*
Posterior medium S	7.6 ± 2.5	6.6 ± 3.2	NS
Posterior large S	9.3 ± 2.2	8.9 ± 3.3	NS
Anterior medium S	7.8 ± 2.4	6.3 ± 2.4	<.02
Anterior large S	9.5 ± 2.1	8.6 ± 2.0	NS

Data are mean ± 1 SD.
S — strength, NS — not significant.

cated by the larger shear forces, larger torques developed at the hip, and larger hip rotations during the beam tasks for the elderly compared to the young.

Frequency of body sway and shear force as indicated by strategy score are related such that as the frequency of sway increases, shear force increases, resulting in a decrease in the strategy score. Thus, the mean group differences between the elderly and young groups discussed above could suggest an increase in the frequency of sway. An alternative explanation for the decreased strategy scores may relate to the possible increase in shear force as the magnitude of sway increases without an increase in sway frequency. It was this issue that was addressed in the clinical analysis of SO strategy scores by normalizing them by the magnitude of sway. Therefore, the differences in strategy score noted for elderly compared to young in the research use analysis (which did not normalize for magnitude of sway) may be an indirect indication of increased sway amplitude. Thus, interpretation of decreased strategy scores relative to excessive upper body movement needs to be made cautiously and with respect to the magnitude of sway.

Head movement cannot be measured by the EquiTest force plate, but it may be of importance in characterizing postural control. The laboratory study results showed that head movement was typically in a direction opposite that of the trunk, implying stabilization of the head relative to the vertical and not relative to the trunk. No significant young-elderly differences were noted in head movement, but the elderly showed a tendency for greater variability in the beam translation task than the young. The clinical importance of this measure is currently unclear. It has been suggested that bilateral vestibular-deficient patients do stabilize the head relative to the trunk rather than to the vertical.[6,17]

The EquiTest data analyzed in the research manner suggest a consistent increase in latency to onset for active COF response to platform translation for the elderly compared to the young. The laboratory study showed the opposite, with the young having longer onset latencies than the elderly. The work by Peterka and Black[15] suggests no age effect for onset latency for active COF response. The differences in the methods between the use of absolute threshold for all subjects used by EquiTest and the use of each subject's pretranslation movement of COF to define a threshold criteria determining the latency used in the laboratory study may influence these results to some extent. The variation in results between the 2 studies and the work of Peterka and Black[15] may simply suggest that any young-elderly differences for healthy groups are small and variable.

The strength (rate of force change) response data from the research analysis of EquiTest, even though this is a measure different from torque, were consistent with those of the laboratory study. Both suggested that at the level of the ankle there were no significant young-elderly rate of force change or torque differences.

The calculation of angular momenta in the laboratory study was used as a measure of instability between individuals or groups in a given task. It is a measure of effort needed to arrest the sway of an individual and so provides information about the effect of a given amount of COG excursion on a subject's stability. Young-elderly differences in angular momenta were found, especially in the beam tasks. This measure is not presently calculated in the EquiTest protocol, but an estimate could be made from the COF information that is measured. Because angular momentum is a direct measure of instability, it may be a useful parameter for both clinical and research use. This measure of instability might be used to compare performance within a given task.

CONCLUSIONS

EquiTest, as it would be used clinically, shows only that the mean elderly performance is different from that of the 20- to 59-year-old group with respect to increased average magnitude of COG sway in two test conditions. Otherwise, the healthy elderly show no clinically significant differences from the normal younger population.

Small but consistent differences are noted in dynamics and implied kinematics for the healthy elderly relative to the healthy young when EquiTest is analyzed in a more detailed research manner. The magnitudes of the differences are condition-specific.

The characterization of the elderly compared to the young by both EquiTest used in a research manner and the laboratory systems appears basically the same, although young-elderly biomechanical differences in postural control were provoked by different tasks in the different studies.

The similarity of findings between the laboratory and EquiTest studies suggests 1) that EquiTest data, when analyzed in a research manner, are sensitive enough measures of the biomechanics of postural control to detect subtle differences in 2 healthy groups and 2) that it is appropriate to infer upper body movement from floor reaction forces, movements of COG from COF, and ankle joint strength from rate of change in COF.

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APPENDIX

Center of Reaction Locations. The dual force plate system incorporates 4 force transducers sensitive to vertical force (see Figure, A). A fifth transducer, sensitive to anteroposterior shear force, is located beneath the pin joint. Center of support surface reaction (COF; alternatively, center of pressure) location is derived from the transducer outputs:

$$PX = \frac{(RF + RR) - (LF + LR)}{(RF + RR + LF + LR)} \times 4.00 \text{ in}$$

$$PY = \frac{(LF + RF) - (LR + RR)}{(LF + RF + LR + RR)} \times 4.20 \text{ in}$$

$$PYL = \frac{(LF - LR)}{(LF + LR)} \times 4.20 \text{ in}$$

$$PYR = \frac{(RF - RR)}{(RF + RR)} \times 4.20 \text{ in}$$

where RF, RR, LF, and LR are the outputs of the 4 vertical force transducers; PX is the medial-lateral location of the COF; and PY, PYL, and PYR are the anteroposterior locations of the COF, respectively for both feet combined, the left foot, and the right foot.

Angle of Sway. Sagittal plane sway angle is calculated from center of gravity (COG) location (see Figure, B), assuming that the body is rotating about the ankle joint as a single rigid link. It is the angle between the vertical and a line from the center of foot support through the COG (see Figure, C):

$$\theta = [\arcsin \frac{PCOG}{HCOG}] - 2.3^\circ$$

where PCOG is the anteroposterior position of the vertical projection of the COG, determined by processing PY through a second-order low-pass filter (see Figure, C), and HCOG is the height position of the COG derived by multiplying the subject's height by 0.55 as shown in the Figure, B.

Sensory Organization Scores. The sensory organization (SO) performance for each of the 6 conditions is evaluated by the calculated equilibrium score (ES):

$$ES = \frac{12.5° - (\theta_{ant} - \theta_{pos})}{12.5°}$$

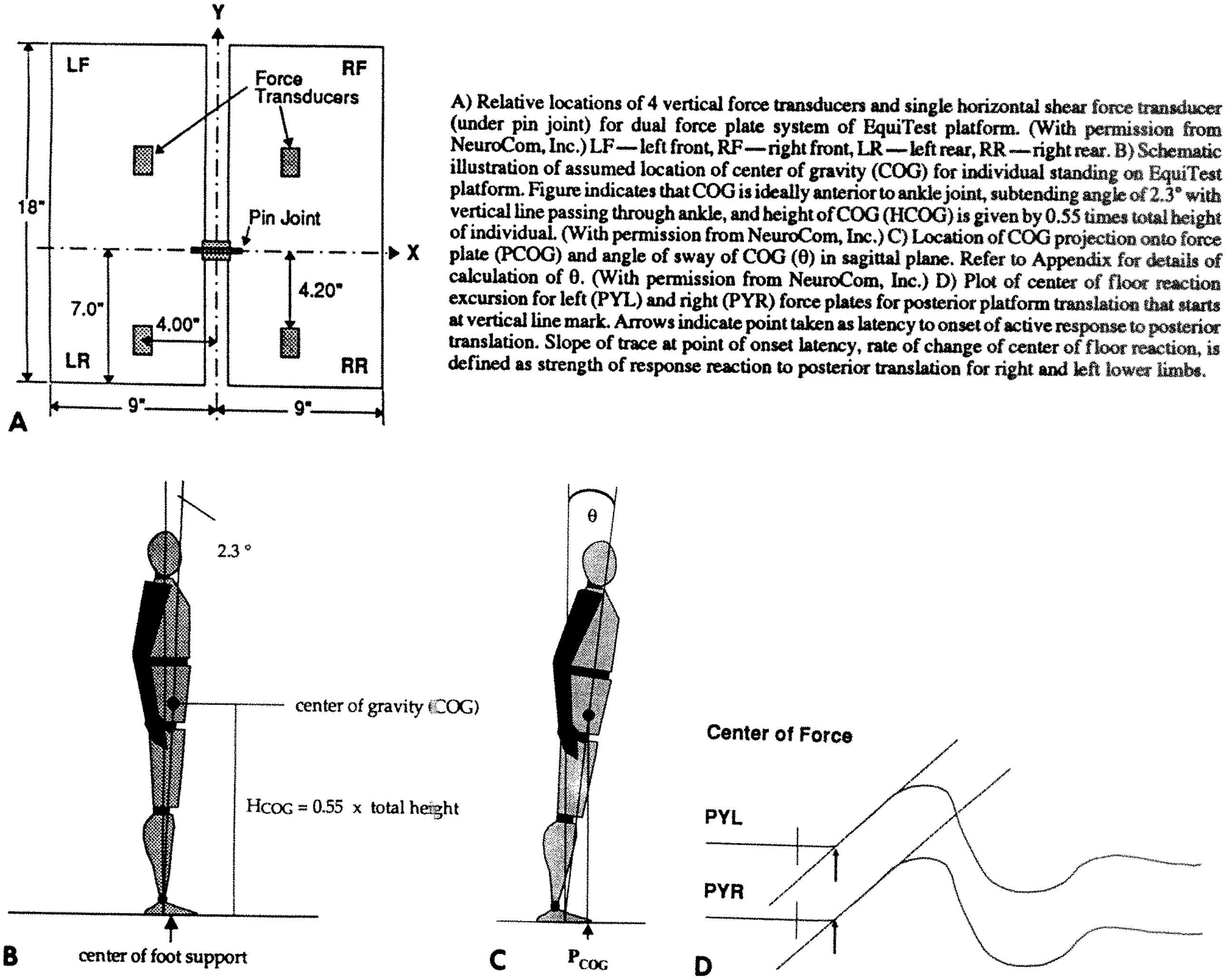
where θ_{ant} is the maximum anterior sway angle during a 20-second trial; θ_{pos} is the maximum posterior sway angle during the same 20-second trial; and 12.5° is the theoretic limit of sway in the sagittal plane for normal stance (θ is defined in the Figure, C).

Movement Strategy Score. Movement strategy score (MS) is calculated in percentage terms as

$$MS = 1 - \frac{(SH_{max} - SH_{min})}{25} \times 100$$

where SH_{max} is the maximum shear force (pounds) over the 20-second SO trial or over the approximately 2-second interval of the platform translations for movement coordination (MC); SH_{min} is the minimum shear force (pounds) for SO and MC; and 25 lb is the average shear force ($SH_{max} - SH_{min}$) generated by a group of normal subjects using a strategy for balancing on a narrow beam that maximizes shear force production as a means of moving the COG.

Response Latency and Response Strength. The Figure, D, shows the procedure for calculation of MC response latency (arrow) and response strength, which is the time rate of change (slope) of the COF trace at this latency, shown by the straight line passing through the latency point.



A) Relative locations of 4 vertical force transducers and single horizontal shear force transducer (under pin joint) for dual force plate system of EquiTest platform. (With permission from NeuroCom, Inc.) LF—left front, RF—right front, LR—left rear, RR—right rear. B) Schematic illustration of assumed location of center of gravity (COG) for individual standing on EquiTest platform. Figure indicates that COG is ideally anterior to ankle joint, subtending angle of 2.3° with vertical line passing through ankle, and height of COG (HCOG) is given by 0.55 times total height of individual. (With permission from NeuroCom, Inc.) C) Location of COG projection onto force plate (PCOG) and angle of sway of COG (θ) in sagittal plane. Refer to Appendix for details of calculation of θ. (With permission from NeuroCom, Inc.) D) Plot of center of floor reaction excursion for left (PYL) and right (PYR) force plates for posterior platform translation that starts at vertical line mark. Arrows indicate point taken as latency to onset of active response to posterior translation. Slope of trace at point of onset latency, rate of change of center of floor reaction, is defined as strength of response reaction to posterior translation for right and left lower limbs.

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DISAPPEARING RECURRENT ACOUSTIC NEUROMA IN AN ELDERLY WOMAN

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Acoustic neuromas have been shown to grow more slowly, if at all, in the elderly. Reduction of tumor size has been rarely reported in intracranial masses thought to be acoustic neuromas. We present a biopsy-proven acoustic neuroma that involuted completely during a 4-year period of surveillance. Possible mechanisms of involution are discussed.

KEY WORDS — acoustic neuroma, aging, cerebellopontine angle, internal auditory canal, neoplasm, spontaneous regression.

INTRODUCTION

Acoustic neuromas of the internal auditory canal and cerebellopontine angle present at almost any age. These tumors tend to grow more slowly in older patients.[1-3] The rates of growth of individual tumors have been documented from serial computed tomography (CT) scans as 0 to 4 mm per year.[1-3] Three cases have been reported in which tumors decreased in size but did not totally involute.[2,4]

We present the case of a biopsy-proven acoustic neuroma that involuted to the extent that it was no longer visible on CT scan. This case is remarkable because it is, to our belief, the first report of total regression of tumor, wherein the identity of the tumor is confirmed, with no apparent cause for the involution.

CASE REPORT

The patient was 60 years old in March 1983, when she presented with vertigo and a mild hearing loss in the left ear. Findings on otoscopic examination were normal. Audiometry showed a speech reception threshold of 30 dB and speech discrimination of 100%. Electronystagmography showed decruitment on the left. Air cisternography showed a 15-mm mass in the left internal auditory canal, protruding 5 mm into the cerebellopontine angle (Fig 1).

In May 1983 the patient's speech reception threshold dropped to 35 dB and her speech discrimination to 68%. She underwent a middle cranial fossa approach to the internal auditory canal, and an inferior vestibular nerve tumor was totally removed grossly. The specimen measured 15 x 8 x 8 mm and the pathologic diagnosis was acoustic neuroma (Fig 2). A postoperative CT scan confirmed the absence of tumor (Fig 3). Postoperatively her speech reception threshold was 40 dB and her speech discrimination rose to 84%. The patient was symptom-free and was able to resume her housework.

Five years later, at 65 years of age, the patient developed motion intolerance. A repeat CT scan in March 1988 showed an 18-mm mass in the left cerebellopontine angle. It was elected to follow this mass with serial CT scans. In September 1988 the next scan showed no change in size (Fig 4A). In June 1989 (Fig 4B) and again in April 1990 (Fig 4C), the mass remained stable.

The patient was 69 years old in January 1992. A CT scan showed no enhancing mass in the cerebellopontine angle (Fig 4D). The fact that contrast material was indeed given is demonstrated by enhancement of the sigmoid sinus and the basilar artery. Further, the patient's chart clearly indicated that contrast material

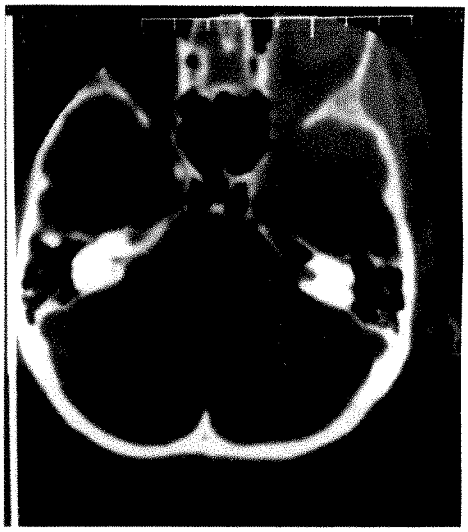

Fig 1. Computed tomography air cisternogram performed in 1983 shows 15-mm intracanalicular lesion that protrudes 5 mm into cerebellopontine angle.

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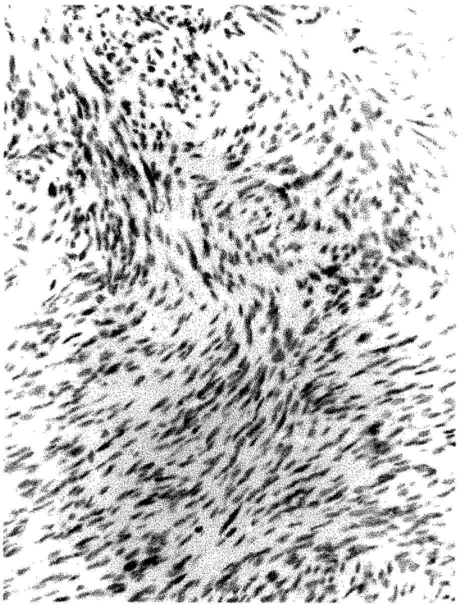

Fig 2. Resected internal auditory canal acoustic neuroma (H & E, original x80). Clearly seen are bipolar spindle cells with elongated oval nuclei. Whorling pattern identifies this tumor as Antoni A. Prominent vascular channels are present.

had been given intravenously.

A magnetic resonance imaging scan with gadolinium was then ordered for the patient to confirm the regression of tumor. She adamantly refused, since she was now totally free of her disequilibrium for the first time in many years.

DISCUSSION

We present a biopsy-proven acoustic neuroma that was resected, recurred, and then spontaneously involuted. This report supports previous studies of partial involutions of acoustic tumors demonstrated on CT scan.[2,4] In these studies the cerebellopontine angle masses were identified as acoustic neuromas by their CT scan characteristics, but were not biopsy-proven. Our study adds to these by reporting a case of a confirmed acoustic neuroma in which spontaneous and total involution occurred.

The medical literature reports numerous cases each year of spontaneous regression and neoplasms. The otologic literature proposes 3 mechanisms of acoustic neuroma involution. One possibility suggested is that the growth of the acoustic neuroma disrupts its already disorganized internal vascularity and causes internal necrosis. The acoustic neuroma tends to contain many vascular channels that can cause both hemorrhage and fibrosis.[4] As these tumors increase in size, they tend to show more vascularity, internal hemorrhage, and degeneration.[5] In this way, the tumor may outgrow its blood supply, leading to central necrosis with involution.[2,4]

A second possible mechanism of tumor involution is disruption of its external blood supply. Supporting this is the observation that tumors that are partially resected tend to grow more slowly than those that are not surgically manipulated.[1,3] The likely mechanism of this postoperative dormancy may be interruption of the internal auditory artery, which is occluded by surgical manipulation in the cerebellopontine angle,[6] and which often is the main blood supply to an internal auditory canal mass.[7] Each of the above explanations seems no more than tentative.

Another mechanism of acoustic neuroma involution is that this tumor's growth characteristics change with the aging process. It has been documented that acoustic neuromas grow more slowly in the elderly population.[1-3] Indeed, in 1 series, occult acoustic neuromas less than 5 mm in size were found in 1% of the population in elderly patients.[8] Tumor regression may be therefore simply an age-related phenomenon.

In this case, it is unlikely that vascular compromise was responsible for tumor necrosis. The tumor had not changed in size for years, and therefore would not have entered into the process of hemorrhage and necrosis seen in enlarging tumors. It is also unlikely that internal auditory artery compression caused this involution. The original tumor was excised in toto, but subsequently recurred to reach the size of 18 mm. Clearly this tumor had adequate blood supply to persist and to enlarge. In addition, the patient's postoperative hearing improvement further indicates that the internal auditory artery was left intact.

This tumor did not initially demonstrate the dor-

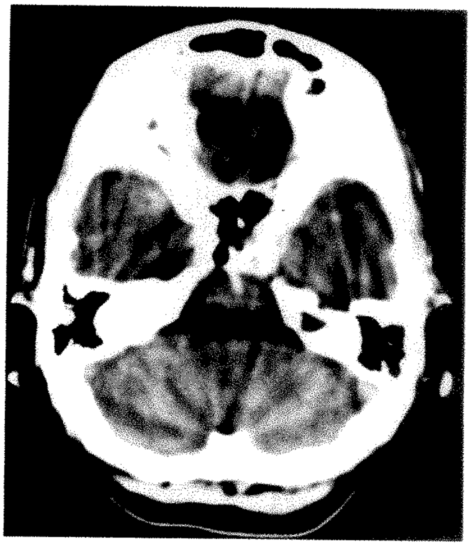

Fig 3. Postoperative computed tomogram (March 1985) with contrast, showing no evidence of original cerebellopontine angle mass.

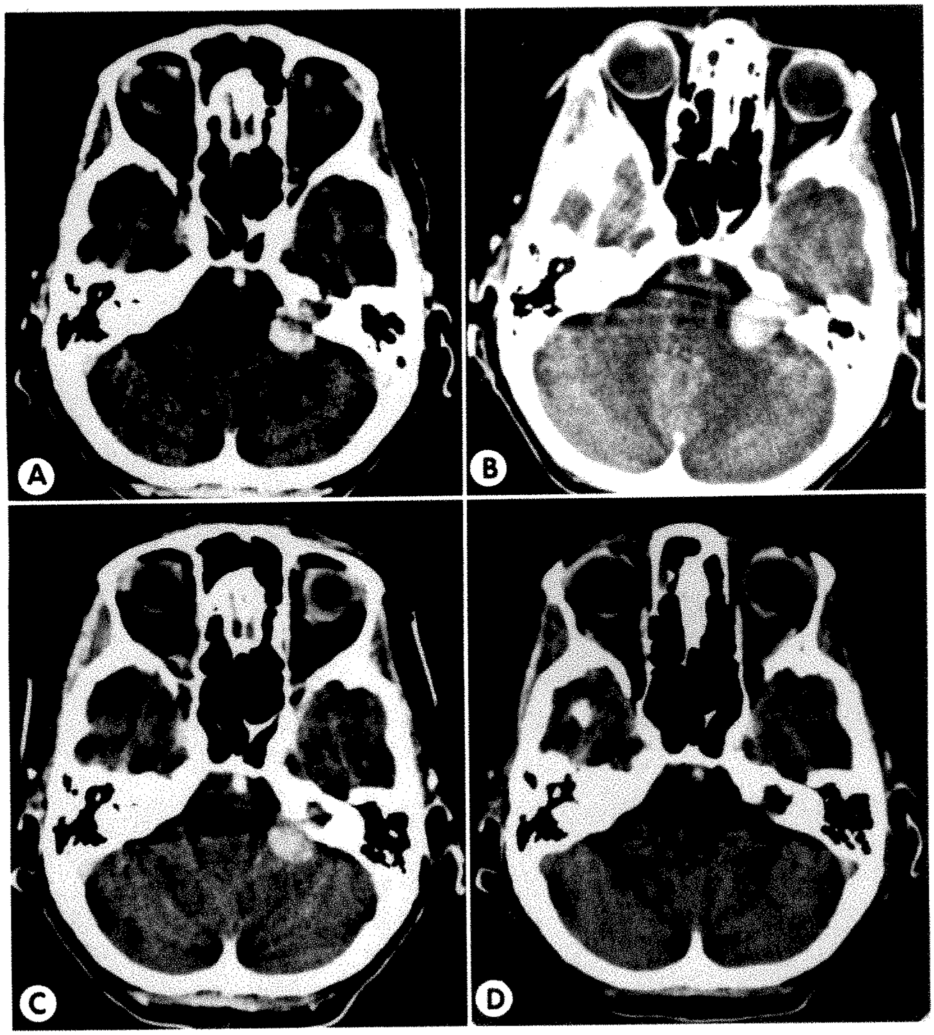

Fig 4. Follow-up computed tomograms taken with contrast medium. A) September 1988 scan shows recurrence of 18-mm size. B) June 1989 scan shows mass still at 18-mm size. C) April 1990 scan shows mass at 18 mm. D) January 1992 scan demonstrates no cerebellopontine angle mass.

mancy usually seen in incompletely excised acoustic tumors. Instead, it grew postoperatively, as has been reported by other authors to be a notable exception to the rule.[1,3,7] Thereafter, however, this mass remained stable for 2 years, only to disappear by 4 years' time. This pattern of growth, dormancy, and regression is suggestive of an intrinsic systemic or immunologic effect. Therefore, we suspect that this involution may be part of the aging process in some individuals, and we suspect that we will see more reports of complete involution in the future as long-term follow-up in older individuals becomes more common.

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THERAPEUTIC EFFECTS OF AN ANTICHOLINERGIC-SYMPATHOMIMETIC COMBINATION IN INDUCED RHINOVIRUS COLDS

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This study's objective was to determine if the combination of pseudoephedrine hydrochloride and atropine sulfate attenuates the symptomatic and pathophysiologic response of individuals to experimental rhinovirus infection when given after illness begins. Forty-three susceptible adult volunteers were challenged with rhinovirus type 39 and randomly assigned to 1 of 2 treatment groups. Twenty-one subjects were treated with the active medication (0.3 mg atropine sulfate and 60 mg pseudoephedrine) and 22 subjects were treated with inert capsules identical in appearance. Treatments were administered 4 times daily beginning approximately 24 hours after rhinovirus challenge and extending for 5 days. Before challenge and on each of 5 treatment days, all volunteers were asked to rate symptom severity and were evaluated for secretion production (weighed tissues), nasal patency (active posterior rhinomanometry), nasal clearance (dyed saccharin technique), eustachian tube function (9-step test), and middle ear status (tympanometry). Twenty subjects in each group were infected with rhinovirus type 39 and were included in the efficacy analysis. Between-group comparisons showed no significant differences in total symptom scores, combined nasal symptom score, secretion production, or the frequencies of persons with eustachian tube obstruction or abnormal middle ear pressures. However, an objective measure of nasal congestion was significantly lower in the active treatment group. The nasal mucociliary clearance rate was significantly more impaired in that group. Side effects consistent with anticholinergic activity were reported more frequently in the active treatment group.

KEY WORDS — atropine, colds, eustachian tube, middle ear, nasal congestion, pseudoephedrine, rhinovirus.

INTRODUCTION

The common cold is an expression of a variety of viral upper respiratory tract infections. Rhinoviruses account for an estimated 40% of these infections.[1] In both adults and children, the high frequency of colds imposes a significant morbidity and an associated economic burden on the population.[2] In rhinovirus colds, the primary infection is believed to be locally limited to the adenoidal, nasal, and nasopharyngeal mucosae.[3] However, in addition to the nasal manifestations of these infections — nasal obstruction, rhinorrhea, and sneezing — complications extend to anatomically contiguous structures, including the lower airway, paranasal sinuses, eustachian tube (ET), and middle ear.[4-8] The wide diversity of rhinovirus subtypes may limit the development of effective vaccines for prevention of these infections, and further, therapeutic trials with a variety of antiviral agents report modest to no effect on the illness despite, in some cases, in vitro activity.[9-13] Consequently, current research has focused on treatment of rhinovirus colds with agents potentially effective in relieving symptoms and preventing sequelae.

Cytotoxicity and/or mucosal disruption are minimal in rhinovirus colds. Most researchers attribute disease expression to secondary effects of the host inflammatory responses. For example, the elaboration of inflammatory substances such as bradykinin, prostaglandin, histamine, and cytokines like interferon, may directly cause disease manifestation, provide positive and negative feedback modulation of inflammation, and activate the parasympathetic nervous system.[13,14] Previous studies have used inhibitors of inflammatory substances and have documented an attenuation of selected symptoms in rhinovirus colds.[15-17] However, a global suppression of the diverse manifestations of rhinovirus infections has not been achieved with single treatment strategies. For example, in studies in patients with colds, oral α-

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adrenergic agents were shown to be effective in reducing nasal congestion,[18-20] and topical parasympathetic antagonists were shown to reduce rhinorrhea.[21-23] Further, data from animal models and limited studies in humans suggest that these agents may be effective in preventing some of the sequelae of viral infections of the upper respiratory tract.[24-30] The present study was performed to evaluate the efficacy of a combination of an oral anticholinergic-antimuscarinic (atropine) and an oral α-adrenergic agonist (pseudoephedrine hydrochloride) in preventing the nasal and otologic responses to rhinovirus infection.

MATERIALS AND METHODS

Experimental Plan. The study was a randomized, double-blind, parallel, placebo-controlled evaluation of the effect of atropine sulfate–pseudoephedrine hydrochloride on the symptomatic and pathophysiologic expression of acute rhinovirus infection. It was approved by the Institutional Review Board of the University of Virginia. Forty-three healthy adult volunteers (18 to 35 years of age) with serum neutralizing antibody titers to rhinovirus type 39 (RV-39) of less than or equal to 2 were enrolled and randomized with respect to treatment. During the week prior to rhinovirus challenge, all volunteers had an otolaryngologic examination and completed 3 baseline evaluations, each consisting of a standardized battery of otolaryngologic tests (nasal patency, nasal mucociliary clearance, ET function, and middle ear pressure). On the day of challenge (study day 0), cold symptoms were evaluated, a blood sample and a nasal lavage were obtained, and RV-39 was administered intranasally. All volunteers reported to a hotel during the afternoon of the day following challenge, and pretreatment symptoms were evaluated at approximately noon. On that day, study medication was administered at 2:00 PM, 6:30 PM, and 11:00 PM. The standardized test battery, excluding assessments of nasal clearance time, was completed during the evening hours. Volunteers were cloistered at the hotel for the next 4 days (days 2 through 5). During the 4 days of cloister, symptoms were recorded at 7:00 AM and study medication was administered at 7:00 AM, noon, 5:00 PM, and 11:00 PM. On each day, nasal passages were lavaged, Kleenex tissues were supplied, used tissues were collected, and the test battery was completed. On the day of discharge (day 6), symptoms were scored, a nasal lavage was performed, and the subjects completed the test battery. Twenty-one days after challenge, blood was collected from all volunteers for determination of convalescent antibody titer to the challenge virus.

Study Medications. Study medications were provided, labeled, and packaged by the inpatient pharmacy at the University of Virginia in accordance with a preestablished randomization scheme. The active drug consisted of a combination of atropine sulfate (0.3 mg) and pseudoephedrine hydrochloride (60 mg) in gelatin capsules. The placebo contained substances in inert capsules of identical appearance.

Virus Challenge. The challenge virus pool was a safety-tested clinical isolate of RV-39 passaged twice in Wistar Institute 38 (WI-38) human embryonic lung fibroblasts. Viral challenges were performed as previously described.[15] Briefly, with the subject supine, 0.25 mL of inocula per nostril was administered intranasally by pipet as coarse drops. The procedure was repeated after a 10-minute waiting period for a total dose of approximately 100 median tissue culture infective doses.

Assessment of Infection and Illness. Rhinovirus isolation from nasal washings performed on study days 0 through 6 and assay of serum neutralizing antibody titers to RV-39 were done by methods previously described.[31] Infection was defined as seroconversion (at least fourfold rise in homotypic antibody to RV-39), or shedding of challenge virus on at least 1 occasion.

The severity of 8 specific symptoms including sneezing, runny nose, nasal stuffiness, malaise, headache, chills, sore throat, and cough were rated by the subject on a 5-point (0 to 4) scale corresponding to none, mild, moderate, severe, or very severe. On the day of discharge (day 6), the subjects were asked if they believed that they had had a cold. For data presentation, the criteria for a cold were a total symptom severity score for the period of the cloister of more than 5, plus either symptoms of nasal discharge for more than 3 days, or the subject's assertion of having had a cold.[15] Nasal secretion weights were determined by previously described methods.[9,13]

Physiologic Measurements. Physiologic measurements included assessments of nasal patency using active posterior rhinomanometry, middle ear pressure using tympanometry, ET function using the 9-step test, and nasal clearance using a modification of the dyed saccharin technique. Nasal clearance was assessed on each of the baseline test days and once daily on days 2 through 6. Rhinomanometry, tympanometry, and ET function tests were performed on each of the baseline test sessions, once daily on days 1 and 6, and 2 (tympanometry, 9-step test) or 3 times daily (rhinomanometry) on days 2 through 5. The variables recorded for each of the tests were inspiratory work per liter (WPL; millijoules [mJ]) for rhinomanometry; middle ear pressure (MEP; millimeters of water) for tympanometry; presence or absence of tubal opening during deglutition for the ET function test; and time to sweet taste (minutes) for nasal clearance function. Methods and instrumentation for these tests are described in detail elsewhere.[15]

Statistical Methods. For analysis, the secretion weight, WPL, clearance time, combined symptom severity score (sum of 8 symptom severity scores), and nasal symptom severity score (sum of runny nose, nasal stuffiness, and sneezing scores) were considered to be continuous variables. Middle ear pressures and the results of the ET function tests were categorized dichotomously as normal or abnormal, according to predetermined ranges. Since past studies showed the responses of the 2 ears of each subject to rhinovirus infection were not independent of each other, the subject was considered to be the experimental unit, and abnormal function for each subject was defined by the presence of either unilateral or bilateral abnormalities. Middle ear pressures were categorized as abnormal if they were greater than or equal to +20 mm H_2O, or less than −50 mm H_2O. For the 9-step tests, results were classified as normal if a change in MEP of at least 10 mm H_2O was observed following any of 4 deglutitions. For each treatment group, means for each test session of the continuous variables were calculated and postinfection means were compared to baseline with a Student's t test (2-tailed, $\alpha \leq .05$). For dichotomous variables, the χ^2 statistic (with Yates correction for continuity) was used for these comparisons. To determine differences in response between treatment groups, the following response variables were calculated for each study subject: total weight of secretions expelled, total nasal symptom severity score and total combined symptom severity score recorded during the period of cloister, and difference between postchallenge and baseline values averaged across test sessions of nasal clearance time and inspiratory WPL. For each continuous variable, the values of the response variables were compared between groups with a Student's t test (2-tailed, $\alpha \leq .05$). For the dichotomous variables, the total number of abnormal observations recorded postchallenge was calculated for each subject. Then, the cumulative distribution of subjects with respect to number of abnormal observations was determined, and the significance of the between-group differences was evaluated with the nonparametric Kolmogorov-Smirnov 2-sample test.

To compare the frequency of adverse reactions in the 2 treatment groups, either a χ^2 statistic (with Yates correction for continuity) or, if appropriate to smaller sample sizes, Fisher's exact test was used. In the descriptive data presentation, the convention of mean ± 1 SD is used throughout.

RESULTS

Infection and Illness. Of the 43 subjects enrolled, 3 were excluded from the data analysis. Two subjects (1 active, 1 placebo) shed a wild virus and 1 placebo-treated subject was not infected, ie, did not shed virus or seroconvert. The remaining 40 subjects (20 per treatment group) either shed virus on at least 1 day (N = 39; 98%; 20 active, 19 placebo) or seroconverted (N = 24; 60%; 14 active, 10 placebo). The average number of days on which the subjects shed virus was 3.3 ± 1.9 days for the placebo treatment group and 4.1 ± 1.4 days for the active treatment group. Twenty-eight (70%) of the 40 infected subjects had a cold. Of these, 13 received the active treatment and 15 received the placebo treatment. None of these differences between treatment groups was statistically significant.

Symptom Relief. On day 1 and prior to the initiation of therapy, the average combined symptom severity score was 2.8 ± 2.0 for the placebo-treated subjects and 2.8 ± 2.3 for the active treatment group. For the 5-day treatment period, the average total combined symptom severity score was not different between the active treatment group (13.7 ± 8.4) and the placebo treatment group (15.7 ± 10.8). Similarly, no significant difference between groups was observed for the average nasal symptom severity score (active 6.2 ± 4.7, placebo 8.2 ± 5.2). For the 8 specific cold symptoms, neither the average baseline severity scores nor the average total severity scores for the posttreatment period were significantly different between the 2 groups. Examination of the daily average severity for each of the 8 symptoms showed a significantly lesser nasal obstruction score in the active treatment group only on day 2 ($p < .03$). No other between-group difference was statistically significant on any study day.

Nasal Secretion. Both secretion weight and tissue counts were less in the actively treated subjects compared to the placebo-treated subjects, although the differences were not statistically significant. Specifically, the average total secretion weights were 9.0 ± 11.7 and 6.8 ± 7.6 grams per 5 days and average tissue counts were 20.3 ± 17.4 and 16.5 ± 14.2 tissues per 5 days in the placebo and active treatment groups, respectively. These 2 measures of secretion production for study subjects were significantly correlated (Pearson coefficient $r = .75$). On all study days, the average secretion weights and tissue counts were less in the actively treated group, but none of the differences were significant. For example, secretion

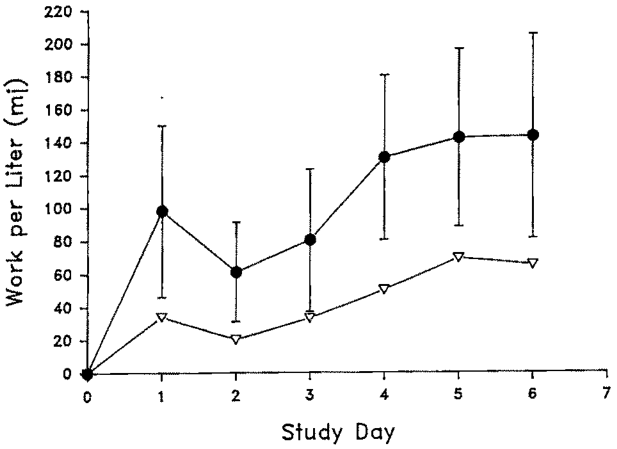

Fig 1. Average increase in inspiratory work per liter referenced to baseline testing of active (triangles) and placebo (circles) treatment groups for each study day. Vertical bars indicate 95% confidence intervals about placebo treatment group means.

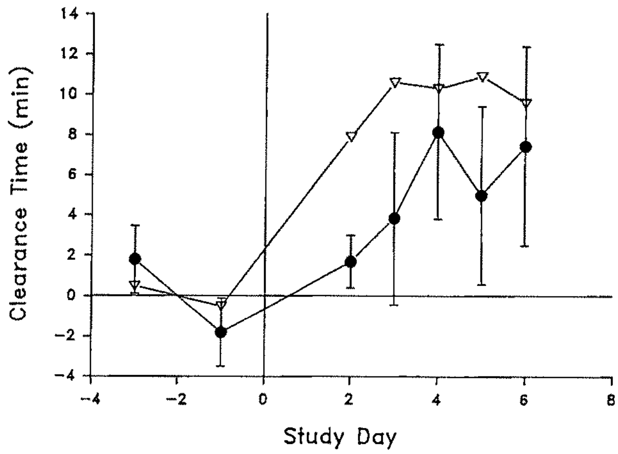

Fig 2. Average increase in nasal clearance time referenced to baseline testing of active (triangles) and placebo (circles) treatment groups for each study day. Vertical bars indicate 95% confidence intervals about placebo treatment group means.

weights for the active and placebo treatment groups were 1.8 ± 3.2 (grams) versus 2.5 ± 3.1; 1.9 ± 2.5 versus 21 ± 3.2; 1.2 ± 1.0 versus 1.6 ± 2.2; 1.0 ± 0.8 versus 1.6 ± 2.3; and 0.9 ± 0.9 versus 1.2 ± 1.6 for study days 1 through 5, respectively.

Nasal Patency. Work per liter is a direct and linear measure of nasal obstruction. Prior to challenge, the average values of this measure for the active (125 ± 55 mJ) and placebo (137 ± 51 mJ) treatment groups were not different. The average daily WPL for the treatment period was significantly less in the active treatment group. Over this period the average increase in WPL was 44 ± 47 mJ for the active and 86 ± 65 mJ for the placebo treatment groups ($p < .05$). Figure 1 shows the average daily, baseline-adjusted WPL for both treatment groups as a function of study day. While both groups of patients showed significant increases in work during the period of treatment ($p < .05$ active, $p < .01$ placebo), the magnitude of the increase in the active treatment group was significantly less compared to the placebo treatment group ($p < .05$).

Nasal Clearance Time. The nasal clearance time is an inverse measure of clearance rate. Prior to challenge, the clearance times were not significantly different between the active (10 ± 5 minutes) and placebo (12 ± 6 minutes) treatment groups. The average clearance time for the postinfection treatment period was 20 ± 5 minutes for the active and 17 ± 6 minutes for the placebo treatment groups. Between-group differences were not significant for this measure. However, the average increase relative to baseline (10 ± 6 minutes active, 5 ± 7 minutes placebo) was significantly different between treatment groups ($p < .05$). Figure 2 shows the baseline-adjusted average clearance times for the 2 groups as a function of study day. Significant prolongations in clearance time for both groups were observed after infection ($p < .05$), with the active treatment group showing an earlier and more extreme response when compared to the placebo treatment group.

Eustachian Tube Function. At entry, the frequency of persons in both treatment groups with good ET function was approximately 80%. Following challenge, these frequencies decreased to approximately 20% on day 1 with a shallow recovery to approximately 40% by days 4 through 6 (Fig 3A). The between-group difference in the frequency of persons with abnormal tubal function was not significant on any study day. For individual persons, the average number of observations with normal ET function on the baseline test days (2.8 ± 0.4 [93%] active versus 3.0 ± 0.2 [98%] placebo) was similar for the 2 treatment groups. For the postinfection test days, the average number of observations with good tubal function was slightly greater in the active treatment group (4.5 ± 3.3; 45%) when compared to the placebo treatment group (3.7 ± 2.8; 37%). However, the cumulative frequency curves for persons in each treatment group as a function of the number of observations of normal ET function were not significantly different (Kolmogorov-Smirnov test, $p > .05$).

Middle Ear Pressure. As previously reported,[4] both positive and negative abnormal MEPs were observed following infection. Using the previously defined criteria, between 85% and 100% of the actively treated subjects, and between 95% and 100% of the placebo-treated subjects had normal pressures on the baseline test days (Fig 3B). For both treatment groups, these frequencies decreased to between 55% and 70% for days 1 through 4 postinfection and then increased. There were no significant differences be-

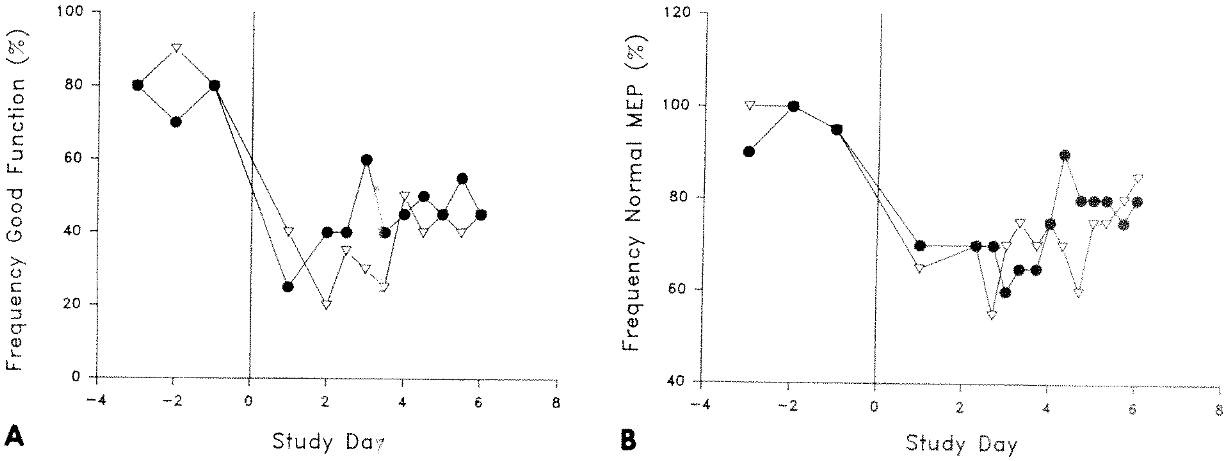

Fig 3. Frequency of persons with A) good eustachian tube function or B) normal middle ear pressures as function of study day for active (triangles) and placebo (circles) treatment groups.

tween groups in the frequency of abnormal MEPs on any study day. The average number of observations with normal MEPs on the baseline test days (2.3 ± 1.0 [77%] active versus 2.5 ± 6 [83%] placebo) was similar for the 2 treatment groups. As with ET function, the average number of normal observations during the postinfection test days was greater for the active treatment group (9.6 ± 3.3; 74%) compared to the placebo treatment group (9.3 ± 4.2; 71%). The cumulative frequency curves for persons in each treatment group as a function of the number of observations of normal MEP were not significantly different (Kolmogorov-Smirnov test, $p > .05$).

Adverse Reactions. Adverse reactions self-reported by the 43 study subjects included dry mouth (54% active versus 23% placebo), light-headedness (36% active versus 5% placebo), fatigue (19% active versus 23% placebo), nervousness (5% active versus 0% placebo), and drowsiness (9% active versus 9% placebo). Differences between groups were significant for light-headedness ($p < .03$) and approached significance for dry mouth ($p < .07$). In addition, 1 subject in the active treatment group reported "rapid heartbeat" and 2 others reported "headrush." Mydriasis was reported by the study nurse for 7 actively treated subjects but no placebo-treated subjects ($p < .05$).

DISCUSSION

Past studies of adult volunteers experimentally challenged with rhinovirus reported that infection results in an early and acute period of sneezing and secretion production with primary expression of symptoms as nasal obstruction, rhinorrhea, sneezing, and malaise.[3] More recent studies have documented an increased nasal obstruction, a decreased nasal ciliary clearance rate, increased frequencies of functional ET obstruction, and abnormal MEPs during periods of active infection.[4,5] This pattern of disease expression also characterized the response of those infected in this study. The magnitudes of functional abnormalities documented by objective measures of nasal patency, ET function, and MEP in the placebo-treated patients agree well with those from past studies.[4,5]

In persons with rhinovirus colds, topical intranasal administration of anticholinergic agents, including atropine methonitrate and ipratropium, has been shown to be effective in reducing secretion weights and symptoms of rhinorrhea.[21-23] Also, an increase in nasal patency in persons with and without colds following both topical and oral administration of α-adrenergic agonists has been documented.[18-20] The primary hypothesis of the current study was that oral treatment of rhinovirus colds with a combination of an anticholinergic and an α-adrenergic agonist would significantly attenuate the major symptoms of nasal obstruction and rhinorrhea. In this study, the expected effect of the α-adrenergic agent was appreciated. Specifically, the increase in inspiratory work performed in moving a liter of air was significantly lessened in the active treatment group. This lesser degree of nasal obstruction measured for the active treatment group was also reflected in their milder nasal obstruction scores. However, while measures of secretion production (including number of tissues used, secretion weights, and symptom scores of runny nose) tended to be less in the active treatment group, the overall reduction in secretion weight was only 24% compared to the placebo group. This lack of treatment effect does not appear to be wholly due to the bioavailability of atropine, since side effects consistent with anticholinergic activity were greater in the active treatment group.[22] Specifically, more than 50% of the subjects in the active treatment group reported dry mouth, and 35% were observed to present with mydriasis. The greater decrease in mucociliary clearance rate in the active treatment group may represent a physiologic manifestation of slowed ciliary beat frequency.[32]

The failure to detect a therapeutic effect consistent with anticholinergic activity may have resulted from the relatively low secretion weights reported by all subjects in this study. Alternatively, the results of 1 recently completed study suggest that the source of nasal secretion in rhinovirus colds is temporally biphasic with an early (peak 2 days), predominantly transudative phase followed by a later phase with an increasing exudative contribution (peak 5 days).[33] The temporal pattern for secretion weights over the transudative phase mirrored that for symptom presentation. Since anticholinergic compounds decrease active glandular secretion, their modulating effect might be most notable in the later period of a rhinovirus cold. A reexamination of the secretion weight data for 2 previous treatment studies with topical anticholinergic compounds showed an effect primarily confined to the later period of rhinovirus infection.[22,23] These data suggest that anticholinergics may not be effective in suppressing the major secretion source for symptoms of runny nose and may be confined in effect to a time period underrepresented in the present study.

Impaired ET function and abnormal MEPs have been observed in children with upper respiratory tract illness of undefined cause[34] and were observed in past studies of adults with experimental rhinovirus colds.[4,5] These debilities are believed to precede the development of otitis media with effusion in children with viral upper respiratory tract infections.[35] If this is correct, therapies that attenuate the responses of the ET and middle ear to viral infection may be useful as prophylaxis against otitis media with effusion. Experimental studies in animal models have documented that the peritubal pressures of the ET are modulated by the autonomic nervous system. Adrenergic stimulation results in a decrease in these pressures, and parasympathetic stimulation results in a pressure increase.[24-26]

In children and adults, improved tubal function was reported following oral administration of α-adrenergic agonists.[28] However, the results for the few studies designed to determine the efficacy of these agents in improving tubal function in patients with colds are not consistent.[27,36] Thus, a secondary objective of this study was to determine if treatment of rhinovirus colds with an α-adrenergic agent reduces the frequency of ET dysfunction and concomitant abnormal MEPs. In this study, subjects infected with rhinovirus showed a significant degree of impairment in their ability to actively dilate the ET with swallowing. Specifically, while approximately 80% of the subjects could perform this function at entry, only about 30% had good function during the course of the infection. Similarly, the frequency of persons with normal MEPs decreased from about 95% on baseline testing to about 70% during the acute period of infection. There were no significant differences between treatment groups in the response of either the ET or middle ear to rhinovirus infection. These data support the results of an earlier study by Virtanen[36] and fail to demonstrate the efficacy of an oral α-adrenergic agent in preventing the ET dysfunction and abnormal MEPs that accompany a rhinovirus cold.

In summary, oral treatment of rhinovirus colds with 0.3 mg atropine sulfate and 60 mg pseudoephedrine hydrochloride 4 times a day did not appreciably diminish a subject's perception of cold symptoms, with the possible exception of nasal congestion. Nor was there a significant effect on objective measures of secretion production, or on the frequency of otologic sequelae, including ET dysfunction and abnormal MEPs. In rhinovirus colds, oral anticholinergic agents, at the doses used in this study, may not be effective in reducing secretion. Second, the reduction in nasal obstruction by α-adrenergics was not observed to benefit the ET. While the lack of a treatment effect for most outcome measures could indicate insufficient bioavailability of the active agents, the occurrence of systemic side effects suggests that increasing dosages would not be advisable. Future studies using these agents in the treatment of colds might focus on topical delivery to the target tissue.

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ORAL BLAST INJURY CAUSED BY AN ACCIDENT

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Blast trauma within the oropharyngeal cavity may be associated with superficial or deep injuries. Superficial injury generally needs only observation; deeper injury that violates the retropharyngeal space may produce dissecting emphysema into the neck and mediastinum followed by prevertebral soft tissue infections and mediastinitis. Injury involving the parapharyngeal space might damage vital cervical vessels. Life-threatening complications may result unless treatment is adequate. Three children who sustained oropharyngeal blast injury are presented. The direct cause was the blast effect of a new, spoiled, orange-flavor beverage just released on the market. The bottle cap of the soft drink and its effervescent liquid "exploded" into their mouths while they were trying to open the bottle with their teeth. Obviously, the failure to observe due precautions, as frequently happens among children, contributed to the occurrence of the accidents. This paper describes the diagnosis, management, and relevant educational and preventive measures of the problem.

KEY WORDS — oral injury.

CASE REPORTS

Case 1. A 13-year-old boy tried to open a 1.5-L plastic bottle of orange-flavor beverage. Since he did not succeed in opening it manually, he attempted to open it with the aid of his teeth. While he was doing so, the cap forcefully hurtled into his mouth, together with a blasting jet of liquid. He suffered from immediate pain and profuse oral bleeding. Examination in the emergency room revealed an apprehensive boy with normal vital signs. Deep lacerations in the oropharyngeal mucous membrane were noted, extending into the hypopharynx. The upper pole of the right tonsil was extensively avulsed, while the left tonsil was lacerated. Both tonsils were actively bleeding. Neck and chest radiographs disclosed pneumomediastinum (see Figure). The patient was taken to the operating room and he underwent bilateral tonsillectomy and drainage of the emphysematous right parapharyngeal space by a Bio-Vac B Flat drain (Biometrix Ltd) directed toward the upper posterior mediastinum and brought out through the pyriform sinus level of the neck. The deep mucosal laceration was sutured. Postoperatively he was treated in the intensive care unit with assisted ventilation for 48 hours and nasogastric drainage for 3 days. Clindamycin phosphate and cefotaxime sodium were given for 5 days. Oral feeding was resumed on the sixth postoperative day. He had an uneventful outcome except for some odynophagia that improved after a few days.

Case 2. A 10-year-old girl sustained an oral blast injury through circumstances identical to those in case 1. Examination in the emergency room 7 hours later disclosed a child in good general condition. Her vital signs were normal, and her body temperature was 38.2°C. Upon examination, tenderness and swelling of the left submandibular area without air crepitation were noticed. Examination of the oropharyngeal cavity revealed that she had sustained mucosal lacerations of the left side of the soft palate and the base of the tongue. The left tonsil had been lacerated and partially avulsed, and was covered with exudate and blood clot without active bleeding. Neck and chest radiographs ruled out air dissection into the soft tissues of the neck and mediastinum. The patient was treated with intravenous clindamycin and gentamicin. Pain, fever, and local swelling persisted for 4 days, then gradual improvement took place. The girl was discharged on a regimen of oral Augmentin to be continued at home. On follow-up of more than 6 months, the patient did not have any medical complaint.

Case 3. An 8-year-old girl sustained an oropharyngeal blast injury from a hurtled bottle cap combined with a jet of fluid in the same circumstances as in cases 1 and 2. On admission to the emergency room her main complaints were pain and odynophagia. Examination revealed no respiratory distress and normal vital signs. A 2-cm nonpenetrating laceration was found above both tonsils with no active bleeding. There were erythema and ecchymosis on the soft palate and pharynx. Neck and chest radiographs were normal. Upon admission she was treated with intravenous clindamycin and gentamicin for 4 days and supplemental intravenous fluids. The wounds healed nicely and antibiotic treatment was stopped. The patient was discharged with no clinical symptoms or complaints.

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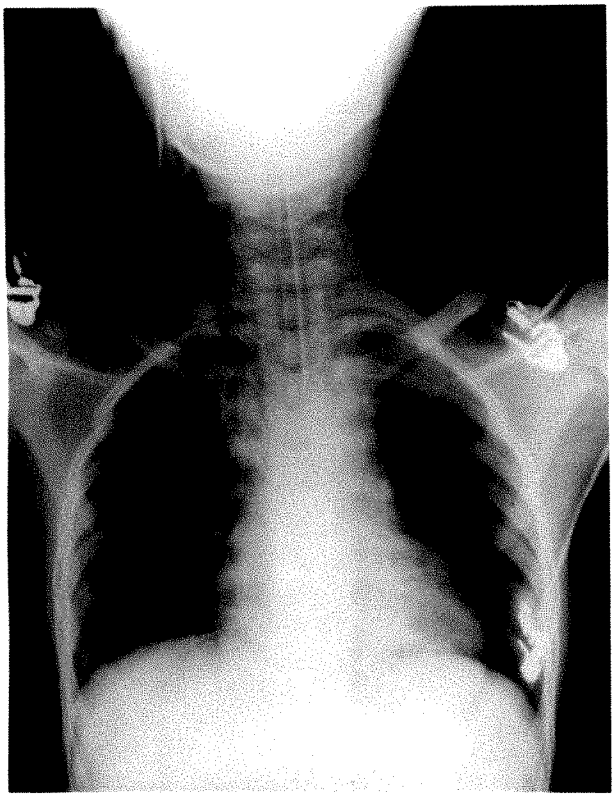

(Case 1) Neck and chest radiograph showing cervical subcutaneous emphysema and air dissection into upper mediastinum.

DISCUSSION

Blunt and penetrating intraoral injuries may involve mucosa alone or deeper structures such as the tonsils, soft palate, or retropharyngeal or parapharyngeal spaces. Violation of the soft palate and the tonsillar pillars might tear the palatine, tonsillar, jugular, or carotid vessels, causing brisk hemorrhage and eventual suffocation. Delayed vascular complications due to blunt trauma such as dissecting aneurysm or thrombosis may follow intimal tears. The thrombus may extend into the brain, leading to diverse neurologic manifestations and eventual neurologic impairment or even death.[1,2]

Laceration of the oropharyngeal wall may induce dissection of air into the planes of soft tissues of the neck and mediastinum following the 3 compartments formed by the cervical fascias. Gravity and intermittent negative intrathoracic pressure favor further propagation of gas and penetration of contents into the mediastinum. Clinically, the injury may be associated with neck and chest pain, odynophagia, and dysphonia; respiratory obstruction and secondary infection are the 2 most threatening complications.[3]

Following oropharyngeal injury, the flora of the mouth gains entry to various tissue planes by direct extension and through descending lymphatics to produce pyogenic infection. Oral pathogenic pyogens, both aerobic and anaerobic, such as *Bacteroides melaninogenicus* (which is almost always found in such wounds), via synergistic activity, may propagate from tonsillar laceration to the sublingual, submandibular, parapharyngeal, or retropharyngeal spaces to the mediastinum. Septic thrombophlebitis of major cervical vessels, mediastinitis, abscesses, pleural effusion and empyema, pericarditis, and airway compression are among the most dreaded complications.[4,5]

Fliss et al[6] reported a case of laceration of the anterior pillar of the left tonsil in an elderly man following an identical pattern of accident as in our 3 cases. Submental, cervical, and mediastinal emphysema ensued. Irwin[7] reported on 2 children, 10 years old, who sustained oropharyngeal trauma caused by lemonade bottle tops that hurtled forcefully into their mouths when they tried to open the bottles with their teeth. One developed significant emphysema as a result of posterior pharyngeal, soft palate, and tonsillar laceration, on top of preexisting acute pharyngitis. The second developed marked edema that necessitated intubation for 48 hours. In the children we present, the cause of blast injury was a newly marketed nonsparkling, orange-flavor beverage. On the bottle it was recommended that the bottle be shaken before consumption. Probably as a result of an inadequate production process, or insufficient or improper preservatives, unintended fermentation took place and gas was produced, increasing the internal pressure within the bottle. Shaking the bottle served to further increase the pressure, rendering cap removal difficult. Evidently, children are particularly unaware of the hazard of opening bottles by means of the mouth, and thus become victims of such accidents.

Blast accidents due to explosion of a sparkling beverage were recorded in the public press in times when family-size glass bottles were marketed. Since the injuries were often devastating, bottles were covered with plastic coating and changed later to plastic bottles. Not rarely, youngsters present after opening beer bottles with their teeth, unaware of a potential blast injury. Evidently, the trauma caused by the hurtled cap, together with the sudden rise of pressure within the oral cavity, led to laceration of the mucosa, avulsion of the tonsils, bleeding, and pneumomediastinum. Hospitalization and strict medical observation are warranted, since it is impossible to predict initially the extent of damage in cases of blast trauma. Bleeding injuries of the lateral or posterior areas of the oropharyngeal cavity may have additional vascular damage.[1,2] Respiratory embarrassment and severe infections may follow soon after.[3,4] Observation, together with diagnostic evaluation, regardless of how benign the injury appears, seems desirable, as many of the grave complications develop insidiously. Oral examination, under general anesthesia when necessary, should be carried out. Vascular bruits, subcutaneous emphysema, respiratory distress, anemia, abdominal distention, and neurologic deficits are to be looked for.

The healing potential of the oropharyngeal mucosa is considerable; therefore, small lacerations need no surgical suture.[8] If necessary, conservative debridement and hemostasis should be carried out under general anesthesia. In the first patient, active bleeding and damage to the tonsils appeared so extensive as to require their removal. In view of the considerable cervical and mediastinal emphysema, a Bio-Vac B Flat drain was left for cervical and mediastinal drainage. Following surgery, the patient was left for 48 hours on assisted ventilation for eventual respiratory obstruction from the severe cervical edema and swelling.

The administration of broad-spectrum antibiotics in these patients is mandatory, since their wounds are prone to suppurative complications in view of the large and various aerobic and oral flora and the bacteria of the fermented beverage itself. Following the present events, the official authorities were promptly notified about the accidents, and soon afterward the incriminated beverage was removed from the market.

Three cases of oral blast trauma are described. All of them occurred in succession during a period of 1 month. A spoiled soft drink and the failure to observe simple principles concerning the correct way of opening bottles combined to cause the accidents.

Although several complications may develop in the course of oral blast injury, they can be treated effectively, providing they are well understood and promptly recognized.

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MIDDLE EAR SUSCEPTIBILITY TO *PSEUDOMONAS* INFECTION DURING ACUTE OTITIS MEDIA

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Pneumococcal otitis media was induced bilaterally, and *Pseudomonas* was inoculated unilaterally into the middle ears of 36 chinchillas to study the pathogenesis of chronic suppurative otitis media. Half of the animals were treated with penicillin prior to *Pseudomonas* inoculation (day 7, late *Pseudomonas*), and half were inoculated with *Pseudomonas* before penicillin treatment (day 3, early *Pseudomonas*). A third group of 18 chinchillas received unilateral *Pseudomonas* inoculation without pneumococcus or penicillin (control). Animals with early *Pseudomonas* were significantly less susceptible to *Pseudomonas* infection in the *Pseudomonas*-inoculated ear than animals with late *Pseudomonas* and controls. Susceptibility to *Pseudomonas* infection in the contralateral ears, which were not inoculated with *Pseudomonas*, was significantly lower in early *Pseudomonas* and control animals than in late *Pseudomonas* animals. Increased susceptibility in the late *Pseudomonas* group might have been due to altered nasopharyngeal microflora or persisting eustachian tube dysfunction — factors that may be important in the pathogenesis of chronic suppurative otitis media in humans.

KEY WORDS — animal model, chronic suppurative otitis media, pathogenesis, *Pseudomonas aeruginosa*.

INTRODUCTION

Chronic suppurative otitis media (CSOM) is a persistent infection of the middle ear accompanied by purulent drainage through a tympanic membrane perforation.[1] It is not an uncommon disease; prevalence rates of 1% have been reported in British and Israeli children.[2,3] The prevalence is greater than 5% among native North American[4] and Pacific Island[5] children. A declining prevalence of CSOM among native North Americans has been attributed to improved medical care.[6]

Microbes associated with CSOM include *Pseudomonas aeruginosa, Staphylococcus aureus*, certain anaerobic bacteria, Enterobacteriaceae, mycobacteria, yeast, and fungi.[7,8] These pathogens are believed to invade the middle ear through a tympanic membrane perforation or tympanostomy tube. Some clinicians believe that inadequately treated or recurrent acute otitis media damages the tubotympanic mucoperiosteum, thereby increasing middle ear susceptibility to opportunistic infection.[9] However, the pathogenesis of CSOM has not been investigated.

Several animal models of CSOM have been developed. Friedmann[10] induced CSOM in guinea pigs by inoculating *P aeruginosa* across the tympanic membrane into the middle ear space; the histopathologic findings closely resembled those of human CSOM,[11] with formation of abundant granulation tissue and cholesteatoma.[10,12] Subsequently, Kenna[13] and Antonelli et al[14] described models of CSOM produced by inoculating *P aeruginosa* into the middle ears of chinchillas. The histologic changes in the chinchilla models also resembled those of human CSOM.

The purpose of this study was to measure the effect of early versus late acute otitis media on middle ear susceptibility to secondary *P aeruginosa* infection in the chinchilla model.

MATERIALS AND METHODS

The *P aeruginosa* strain was isolated from a 31-year-old woman who presented to the St Paul Ramsey County Hospital Otolaryngology Service with CSOM. The strain was passed serially in mice by intraperitoneal inoculation to enhance virulence and was frozen. Exotoxin production was analyzed by Dr Barbara Iglewski, University of Rochester Medical Center, and was similar to that of previously studied strains, eg, PAO.[15] For chinchilla inoculation, an aliquot was thawed and subcultured on sheep blood agar (SBA),

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Presented in part at the Association for Research in Otolaryngology Fourteenth Midwinter Meeting, Clearwater Beach, Florida, February 3-7, 1991, and the Fifth International Symposium on Recent Advances in Otitis Media, Fort Lauderdale, Florida, May 20-24, 1991.

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EXPERIMENTAL TIMETABLE

		Day(s) Procedures Performed		
Group	*No.*	*Pneumococcus Inoculation*	*Penicillin Treatment*	Pseudomonas *Inoculation*
Late *Pseudomonas*	18	0*	3-7	7
Early *Pseudomonas*	18	0	3-7	3
Control	18	ND	ND	0

*Day 0 is first experimental day.

ND — not done.

and representative colonies were grown to midlog phase (6 hours) in brain-heart infusion broth (Difco, Detroit, Mich) at 37°C. The concentration was determined by measuring optical density (OD) at 630 nm and interpolating colony-forming units (CFU) per milliliter from a predetermined linear OD-CFU regression. The culture was then serially diluted to final concentrations between 200 and 3,000 CFU/mL in sterile phosphate-buffered saline (PBS; pH 7.4). A pilot study indicated that the inoculum range of 20 to 300 CFU produced *Pseudomonas* otitis media in approximately 75% of normal chinchillas. In this study, animals were inoculated in 4 batches, with 4 or 5 animals per experimental group. Actual inocula were 25, 62, 160, and 300 CFU per ear. After determining that there was no difference in response within this dose range, data for all groups were collapsed for further analysis.

Type 7F (American type 51) *Streptococcus pneumoniae*, provided by R. Austrian from a patient with bacteremia, was inoculated intraperitoneally in mice to enhance virulence. The virulent strain was subcultured on SBA, from which 5 to 10 colonies were suspended in Todd Hewitt broth (Difco) supplemented with 3.5% bovine albumin and grown at 37°C to midlog phase (4 to 6 hours). The suspension OD was read at 630 nm; and the bacterial concentration (CFU per milliliter) was interpolated from a previously determined OD-CFU regression. The suspension was washed in PBS and diluted to 400 CFU/mL. The actual concentration of the suspension was determined by quantitating CFU; a volume of 0.1 mL was inoculated into middle ears.

Pseudomonas organisms and pneumococci were inoculated by inserting a 15-gauge needle into the superior bulla, through which a sterile polyethylene catheter was passed into the inferior bulla, and injecting the bacterial suspension with a tuberculin syringe.

Healthy 1- to 2-year-old chinchillas weighing between 400 and 600 g were used. All were culled from breeding stock because of poor breeding activity or fur defects. Animals were anesthetized with intramuscular (IM) ketamine hydrochloride, 30 mg/kg, prior to all procedures and examinations.

Animals were randomized to 1 of 3 study groups after determining that their middle ears were normal by otoscopy and tympanometry. Pneumococcal otitis media (POM) was induced bilaterally in 2 groups of chinchillas (see Table). In both groups, POM was allowed to develop for 3 days prior to initiating penicillin treatment or inoculating *Pseudomonas*. In the "early" *Pseudomonas* group, 18 animals were unilaterally inoculated with *Pseudomonas* on day 3 following pneumococcal inoculation, and thereafter they received 5 daily IM injections with 50,000 U procaine penicillin G (Eli Lilly, Indianapolis, Ind). In the "late" *Pseudomonas* group, 18 animals received 5 days of penicillin therapy beginning on day 3 following pneumococcus inoculation; after completion of treatment (on day 7), *Pseudomonas* was inoculated into 1 middle ear. Hence, "early" and "late" refer to the relative points in the course of POM at which animals were inoculated with *Pseudomonas*. Chinchillas in the control group (n = 18) were also unilaterally inoculated with *Pseudomonas*, but did not receive pneumococcus or penicillin.

Otomicroscopy and tympanometry were performed on day 3 after pneumococcus inoculation, and on the first 3 days and at weekly intervals for 3 weeks after *Pseudomonas* inoculation. Otomicroscopy was performed after gently aspirating drainage from the external canal, taking care to avoid contact between the suction tip and the tympanic membrane. The status of the tympanic membrane was scored as follows: 0 for normal; 1 for gray or white, opaque; 2 for red, translucent; 3 for red, opaque; 4 for yellow, translucent; 5 for yellow, opaque; and 6 for perforation.[16] *Pseudomonas* otitis media was defined as inflammation of the tympanic membrane (score > 2) with *Pseudomonas* isolated in either pure or mixed culture from middle ear fluid (MEF). Spontaneous perforation was defined as a visible defect in the tympanic membrane in the absence of any trauma, or tympanometry yielding a static admittance of ≤ 2 millimhos in the presence of otorrhea. Any animal with head-tilt posturing or ataxia was classified as having labyrinthitis.

Cultures of the middle ears, blood, nose, and external auditory canals were performed on day 3 following pneumococcal or *Pseudomonas* inoculation, after completing penicillin treatment, and at weekly intervals. Samples from the nose and both external auditory canals were obtained with a calcium alginate swab and streaked on SBA. Samples of MEF were aspirated through a polyethylene catheter

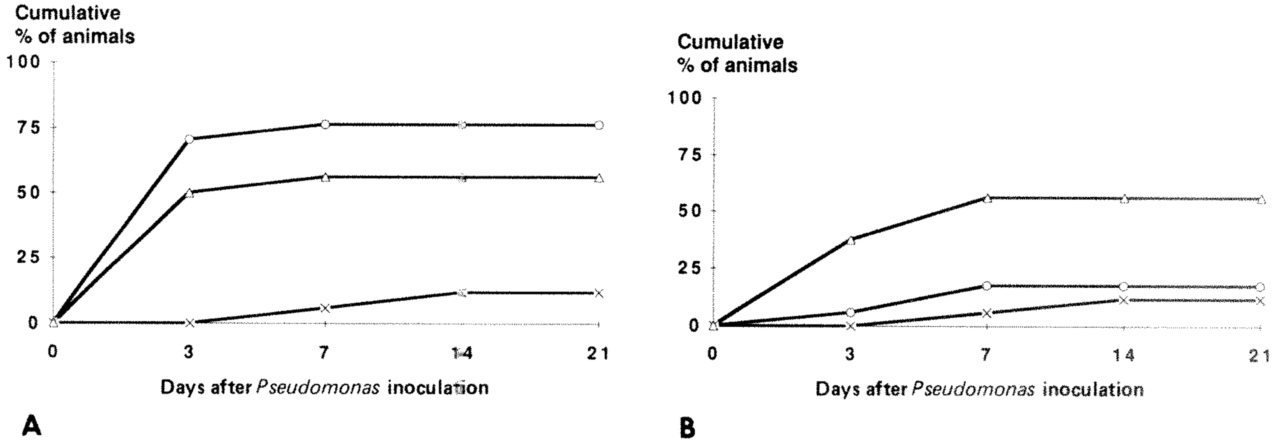

Fig 1. Cumulative percentages of animals from which *Pseudomonas aeruginosa* was cultured as function of time following inoculation of *P aeruginosa* into middle ear. Circle — control, triangle — late *Pseudomonas*, cross — early *Pseudomonas*. A) From *Pseudomonas*-inoculated middle ear (ipsilateral). B) From middle ear not inoculated with *Pseudomonas* (contralateral).

and carefully passed from the superior to the inferior bulla to avoid trauma to the tympanic membrane, as described above. A second 23-gauge needle vented the superior bulla to prevent tympanic membrane perforation during aspiration. Otomicroscopy was repeated after aspiration to document tympanic membrane integrity. Blood was sampled via cardiocentesis and cultured on SBA and in thioglycollate broth, from which a subculture onto SBA was taken after a 24-hour incubation at 37°C. Agar cultures were incubated overnight in 10% carbon dioxide. Speciation was performed by standard microbiologic techniques.

A χ^2 test was used to test the significance of differences in frequency percentages between groups.

RESULTS

One control animal died of anesthetic complications prior to *Pseudomonas* inoculation. Two late *Pseudomonas* animals and 1 early *Pseudomonas* animal died of pneumococcal sepsis, meningitis, or pneumonia before *Pseudomonas* inoculation. These 4 animals were not included in the statistical analysis.

All MEF samples from the 36 pneumococcus-inoculated animals were culture-positive for pneumococcus on day 3 after pneumococcus inoculation. Treatment with 5 days of procaine penicillin G effectively eliminated pneumococcus from the MEF of all ears in both treatment groups.

In the *Pseudomonas*-inoculated ears, *Pseudomonas* otitis media developed in 76% (13 of 17) of control animals, 56% of late *Pseudomonas* animals (9 of 16), and only 12% of early *Pseudomonas* animals (2 of 17) within 21 days after inoculation (Fig 1A). These differences were highly significant ($p < .001$; $\chi^2 = 14.89$, df = 2). By 21 days after inoculation, *Pseudomonas* otitis media developed in the uninoculated ears of 56% (9 of 16) of late *Pseudomonas* animals, 18% (3 of 17) of control animals, and 12% (2 of 17) of early *Pseudomonas* animals (Fig 1B). These differences were also highly significant ($p < .01$; $\chi^2 = 9.46$, df = 2). Spontaneous tympanic membrane perforations developed in all cases of *Pseudomonas* otitis media, usually within 2 days after the development of *Pseudomonas* infection (Fig 2A). None of the ears with pneumococcal infection alone spontaneously developed tympanic membrane perforations.

Pseudomonas was not isolated from the external auditory canals until *Pseudomonas* otitis media and spontaneous tympanic membrane perforation had occurred. *Pseudomonas* was not cultured from the nose of any chinchilla prior to inoculation, but was isolated from nasal cultures within 3 days after inoculation in 60% of late *Pseudomonas* and control animals. It was isolated from the nose of 40% of chinchillas with early *Pseudomonas*, but not during the first 7 days after inoculation (Fig 2B).

Signs of labyrinthitis developed in 14% of the late *Pseudomonas* animals and 35% of the control animals, but in none of the early *Pseudomonas* animals. This difference was significant ($p = .02$; $\chi^2 = 8.093$, df = 2; Fig 2C).

Survival after the development of *Pseudomonas* otitis media was usually less than 1 week (Fig 2D). These animals succumbed to *Pseudomonas* sepsis, pneumonia, or meningitis. Four of 17 early *Pseudomonas* animals and 3 of 16 late *Pseudomonas* animals that did not have *Pseudomonas* otitis media, but had *Pseudomonas* isolated from the nose, also died with *Pseudomonas* sepsis.

DISCUSSION

Pseudomonas is an opportunistic pathogen that usually causes disease in patients with significantly compromised host defenses — for example, by burns

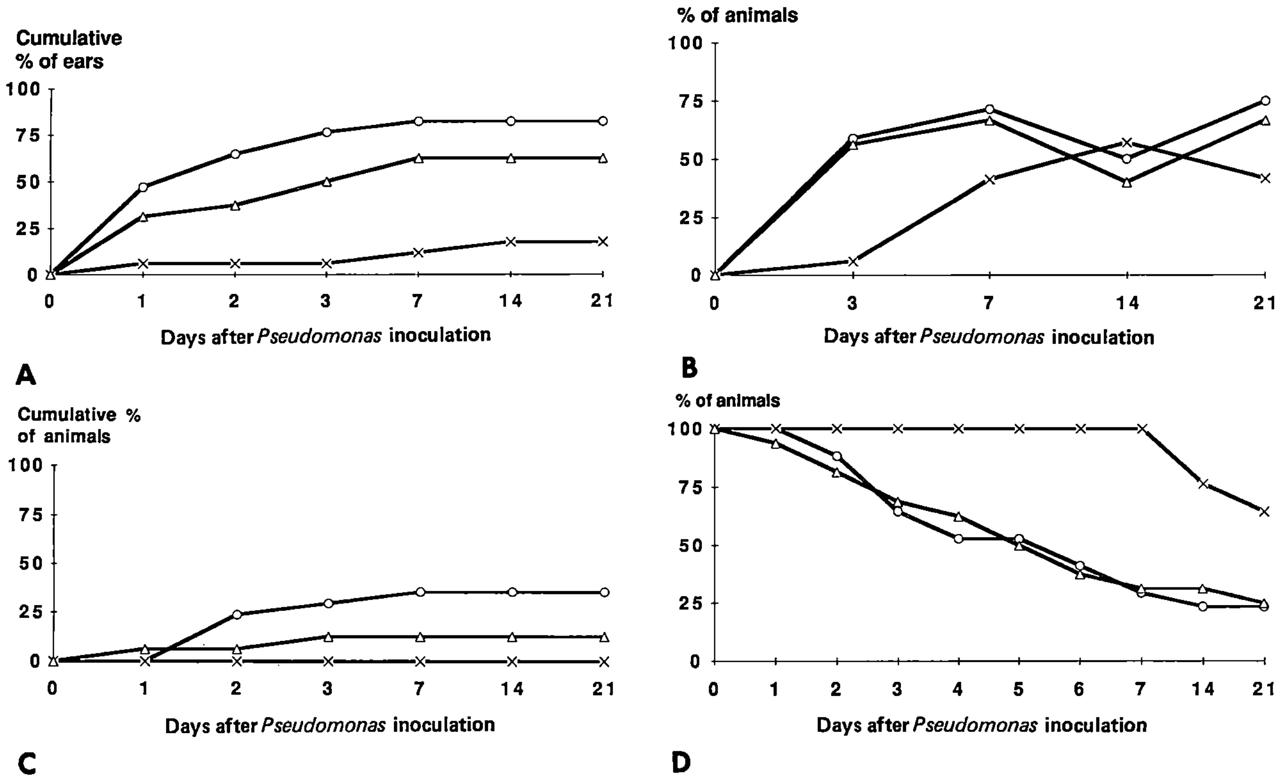

Fig 2. Other findings following *Pseudomonas* inoculation of middle ear. Circle — control, triangle — late *Pseudomonas*, cross — early *Pseudomonas*. A) Cumulative incidence of spontaneous tympanic membrane perforation. B) Point prevalence of *Pseudomonas* colonization of nose. C) Cumulative incidence of labyrinthitis. D) Survival.

or cystic fibrosis.[17] Pneumococcal otitis media causes damage to the tubotympanic mucoperiosteum,[18,19] and would presumably increase susceptibility to secondary *Pseudomonas* otitis media. In contrast, we observed that *Pseudomonas*-inoculated ears of animals that were inoculated early in the course of POM were less susceptible to *Pseudomonas* middle ear infection than animals that were inoculated late, following treatment of POM, or healthy animals without POM.

Pneumococcal otitis media stimulates a strong host response, with recruitment of leukocytes and production of inflammatory mediators.[18-20] This host response diminishes with antibiotic treatment of the POM.[20] Both the lower susceptibility to secondary *Pseudomonas* infection and the lower incidence of labyrinthitis in early *Pseudomonas* animals may have been due to enhanced host defenses, stimulated by pneumococcus, that were not yet modulated by penicillin treatment.

Tympanic membrane perforations or tympanostomy tubes are thought to be essential elements in the pathogenesis of CSOM. We found that tympanic membrane perforations developed *after* the onset of *Pseudomonas* otitis media — an observation we previously reported.[14] Likewise, Vartiainen et al[21] reported that patients with *Pseudomonas* CSOM have higher rates of developing tympanic membrane perforation after mastoidectomy and tympanoplasty than patients with CSOM caused by other pathogens. Most strains of *P aeruginosa* produce alkaline proteinase and elastase, which degrade collagens and elastin,[22-24] key structural components of the tympanic membrane. Therefore, tympanic membrane perforation seems to be the result rather than the prerequisite for development of *Pseudomonas* middle ear infection.

The increased susceptibility of the uninoculated or contralateral middle ears of late animals to *Pseudomonas* infection was the most surprising finding of this study. The contralateral ears of early and control animals had low susceptibility to *Pseudomonas* infection. Others have also reported low rates of contralateral *Pseudomonas* otitis media in animals without preexisting otopathology.[10,13,14] Since *Pseudomonas* was present in the nose soon after middle ear inoculation and in the external auditory canal only after spontaneous tympanic membrane perforation, *Pseudomonas* probably entered the contralateral middle ear via the nasopharynx and eustachian tube.

It is unclear which factors were specifically responsible for the increased susceptibility of contralateral late middle ears to secondary *Pseudomonas* infection. The chinchilla middle ear inflammatory response to POM wanes within days of initiation of penicillin treatment[20]; however, eustachian tube dysfunction, as evidenced by resolution of middle ear effusion, may take much longer to resolve.[25] *Pseudomonas aeruginosa* produces proteases[26] and pyocyanin,[27] which disrupt respiratory epithelium ciliary activity, an important component of eustachian tube function.[28] Hence, persistent eustachian tube dysfunction with relatively weak tubotympanic defenses would seem to favor middle ear invasion by opportunistic pathogens.

Penicillin treatment may also have contributed to the high susceptibility of contralateral ears of late animals to *Pseudomonas*. Antibiotic therapy for acute otitis media alters the pharyngeal microflora in humans.[29] Such alterations in the commensal microflora allow more resistant opportunistic pathogens (eg, *P aeruginosa*) to colonize the upper respiratory tract,[29] and thereby predispose to infection.[17] Although nasal cultures were taken throughout the course of this experiment, rigorous surveillance of the commensal flora was not performed. Animals with untreated POM and animals with penicillin treatment without POM were not studied in this experiment, so the isolated effects of POM and penicillin treatment could not be assessed. Since antibiotics are the first line of treatment for acute otitis media and for prophylaxis of recurrent acute otitis media in the United States, further studies should be done to determine whether antibiotic use may contribute to the development of CSOM.

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AUDIOLOGICAL STUDY IN GUINEA PIGS WITH TYPE I ALLERGY INDUCED IN THE INNER EAR

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Time course studies of electrocochleography and the auditory brain stem response were performed in guinea pigs that were passively sensitized by sera containing antidinitrophenyl reaginic antibody and specifically challenged by dinitrophenyl–bovine serum albumin injected through the stylomastoid foramen. A negative summating potential on electrocochleography was observed from 12 to 48 hours, but not at 72 hours, after the specific challenge. A threshold increase on the auditory brain stem response was observed 15 minutes after the specific challenge; the threshold recovered to the prechallenge level within 7 days. Further, we used Tranilast, a blocking agent of chemical mediator release from mast cells, before the specific challenge. A negative summating potential and head deviation were not observed after the use of this agent. These results suggest that the auditory change provoked in the inner ear of the sensitized guinea pig may have been induced by type I allergy.

KEY WORDS — auditory brain stem response, electrocochleography, inner ear, Tranilast, type I allergy.

INTRODUCTION

In a previous report, Miyamura et al[1] documented that head deviation, nystagmus, and negative summating potential (SP) in electrocochleography (ECochG) were provoked in guinea pigs that had been passively sensitized by sera containing the antidinitrophenyl (anti-DNP) group reaginic antibody and specifically challenged by DNP coupled with bovine serum albumin (BSA). Reversible auditory disturbances and dysequilibrium, which are characteristically observed in Meniere's disease, may be provoked by a reagin-mediated reaction (type I allergy). The relationship between allergy and Meniere's disease has been reported by many authors,[2-12] and some of them have stated that type I allergy may cause this disease.[5-12] But there have been few basic studies on the pathogenesis of type I allergy. To approach this issue, we performed a time-course study on auditory testing, including auditory brain stem response (ABR) and ECochG, in sensitized animals.

MATERIALS AND METHODS

Animals. Male Hartley guinea pigs ranging in weight from 300 to 400 g were used in this investigation. The animals displayed a normal Preyer's reflex.

Antigens. We used DNP-coupled ascaris extract (DNP-Asc) to immunize the animals. The final concentration of DNP in the DNP-Asc conjugates was 2.1×10^{-4} mol/L. Also, DNP was conjugated to BSA according to the method of Eisen et al.[13] The BSA was purchased from Sigma (St Louis, Mo). These conjugates were used for specific challenge to the sensitized animals.

Preparation of Antisera for Passive Sensitization. We mixed DNP-Asc (5 µg) and aluminum hydroxide gel (5 mg) and adjusted them to a total volume of 1.0 mL, and this mixture was injected into the foot pads of the guinea pigs. Aluminum hydroxide gel was prepared by the method of Levine and Vaz.[14] Four weeks later, the same amount of the mixture was injected intracutaneously into the backs of the guinea pigs, and this booster injection was repeated 3 times per month. One week after the last booster injection, sera were obtained and tested for the production of anti-DNP reaginic antibody by the homologous passive cutaneous anaphylaxis (PCA) reaction. The 7-day PCA titers against DNP were above 1,280x.

Passive Sensitization. Ten guinea pigs to be used for ECochG testing, and 5 to be used for ABR testing, were passively sensitized with an intravenous injection of 1.0 mL of antisera.

Local Challenge to Inner Ear. One week after passive sensitization, animals were anesthetized under sodium pentobarbital (15 mg/kg) general anesthesia, and 1% lidocaine was used for local anesthesia; then a postauricular incision was made to expose the stylomastoid foramen. The DNP-BSA (0.02 mL, containing 0.1 µg DNP) was then injected through the stylomastoid foramen into the facial nerve. In the same manner, physiologic saline (0.05 mL) was injected into 5 passively sensitized and 5 nonsensitized animals, which served as control groups.

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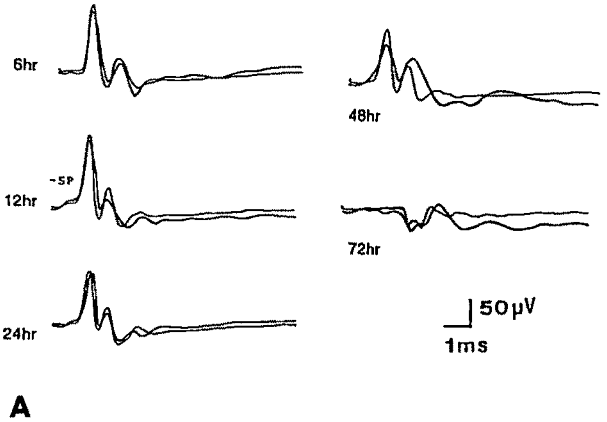

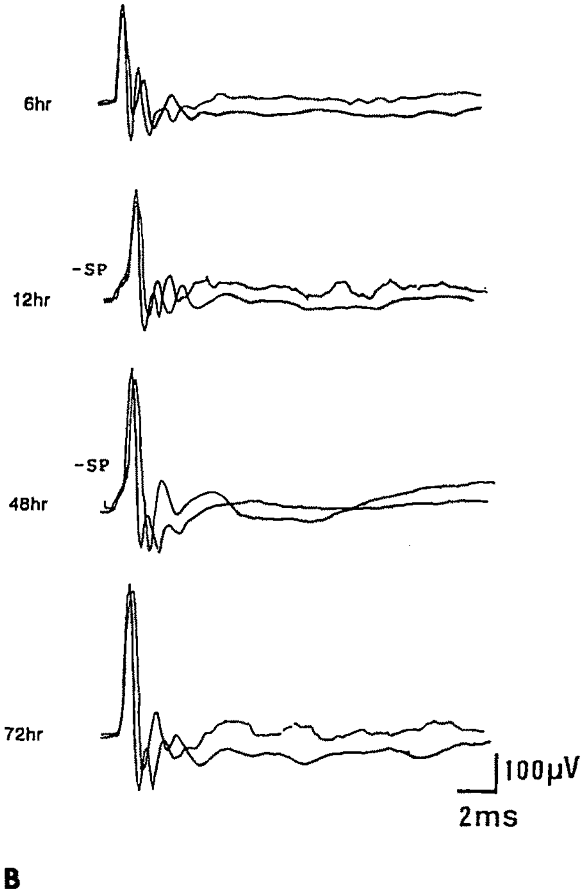

Fig 1. Electrocochleograms of each period in 2 of 8 animals in which negative summating potential (SP) was observed after challenge. A) In this animal, negative SP appeared at 12 hours, and disappeared at 24 hours after challenge. B) In this animal, it appeared at 12 hours and disappeared at 72 hours.

Auditory Testing. We performed ECochG periodically (6, 12, 24, 48, and 72 hours) after the local challenge in the 10 sensitized animals. Three other animals were treated with Tranilast (50 mg/kg), a drug that inhibits chemical mediator release from mast cells without antihistaminic effects.[15] Tranilast was administered by intraperitoneal injection 2 hours prior to the local antigen challenge, and ECochG was then performed in the same manner.

The ECochG was performed with the active electrode on the round window, the reference electrode on the retroauricular temporal bone, and the ground electrode on the forehead. A silver–silver chloride ball tip was used as the active electrode; and stainless steel needles with epoxy coating, except on the 0.5-mm tip, were used as reference and ground electrodes.

Stimulation was repeated 100 times with 110 dB sound pressure level single sine wave clicks of 2,000, 4,000, and 8,000 Hz derived from a TDH-39 earphone by the open method at 1 cm from the tested ear. Electrical responses were amplified by a physiologic response recorder (MEB-3102), with the recording system filter set at 100 to 3,000 Hz and averaged by an averager (DAT-3202).

The ABR was also investigated periodically (15 minutes; 1, 2, 12, 24, and 72 hours; and 7 days) after the local challenge in the sensitized and nonsensitized animals, with the active electrode positioned at the vertex, the reference at the test ear, and the ground at the contralateral ear. The impedance of each electrode was 3,000 Ω or less. The ABR was recorded by a Cadwell CA-5200 instrument using 200 single sine wave clicks of 2,000 Hz and a filter setting with a 30- to 3,000-Hz band pass. Stimulation started with an intensity of 100 dB hearing level (HL) and was decreased by 10-dB steps until no ABR components were present. All of the responses of ECochG and ABR were recorded at least twice.

We also investigated head deviation and nystagmus in 40 sensitized guinea pigs; 15 of these animals were treated with an intravenous injection of Tranilast (50 mg/kg) prior to the local challenge.

Nystagmus was recorded by AC nystagmography using needle electrodes inserted into the median and lateral canthi of the left eye. Head deviation was determined by its continuity and by accompanying nystagmus. In the animals without nystagmus, deviation was determined by a swimming test. Each guinea pig was put in a pool to swim 3 times, and swimming toward the same side all 3 times was considered to show deviation.

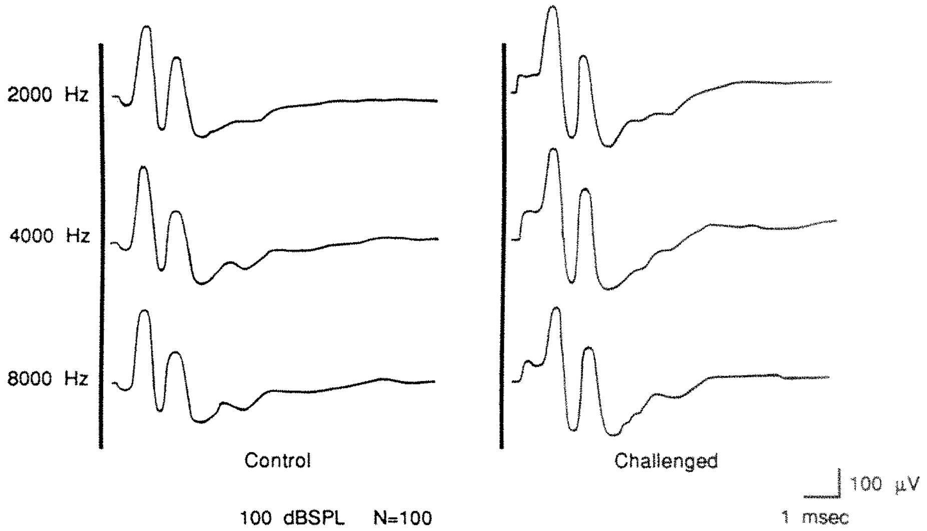

Fig 2. Electrocochleograms taken at 2,000, 4,000, and 8,000 Hz before and after challenge. Before challenge, we observed no differences in whole nerve action potentials at each frequency. After challenge, we observed no differences in negative summating potential at each frequency.

RESULTS

Electrocochleography. A negative SP was observed in 8 of the 10 sensitized animals. Decrements of whole nerve action potentials were also observed in 2 of the 10 sensitized animals. We were able to investigate ECochG at several points in time in 6 of these 8 animals. A negative SP was observed from 12 to 48 hours, but not at 72 hours, after the challenge. Figure 1 shows the ECochG of 2 of these 6 animals at each period.

Figure 2 shows the ECochG of 1 of these 6 animals at 2,000, 4,000, and 8,000 Hz before and after the challenge. Generally, we observed no difference in whole nerve action potentials at each frequency before the challenge, and no difference in negative SP at each frequency after the challenge.

We then tested 3 sensitized animals with Tranilast (50 mg/kg) prior to local challenge. No negative SP was observed in any of these 3 animals, even at 12 and 24 hours after local challenge. Figure 3 shows the ECochG of 1 of these animals at 12 and 24 hours after the challenge.

Auditory Brain Stem Response. We could record all ABR waves in all 5 animals before local challenge and in 4 of these 5 animals after the challenge; 1 of these animals was excluded because of anaphylactic shock. Figure 4 shows the threshold changes in a sensitized animal after local challenge. The thresholds began to increase within 15 minutes and reached maximum levels at 12 hours. They began to decrease between 12 and 24 hours after the challenge, and were returned to the prechallenge level 7 days after the challenge. Generally, the threshold changes ranged from 40 to 50 dB at 12 hours, 20 to 30 dB at 24 hours, and 0 to 10 dB at 7 days after challenge. Figure 5 shows the ABR waveforms at 100 dB HL of 1 of the 5 sensitized animals at each period. Changes in the latency-intensity curves of wave I on the ABR in 2 of the 5 sensitized animals are shown in Fig 6. Similar to the thresholds, the peak latency of wave I increased for a short time after the challenge. The recovery of the latency at 24 hours was dominant at 90 and 100 dB HL. Generally, increments of the peak latency of wave I at 90 dB HL ranged from 0.55 to 0.7 milliseconds at 15 minutes, 0.8 to 0.9 at 1 hour, 0.85 to 1.15

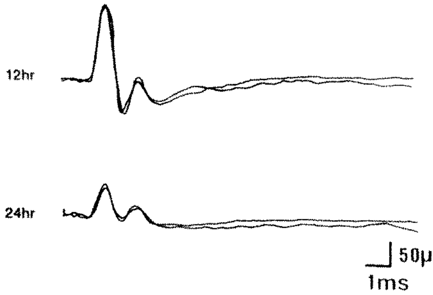

Fig 3. Electrocochleograms of 1 of 3 animals that were given Tranilast prior to specific challenge. None of these 3 animals showed negative summating potential after challenge.

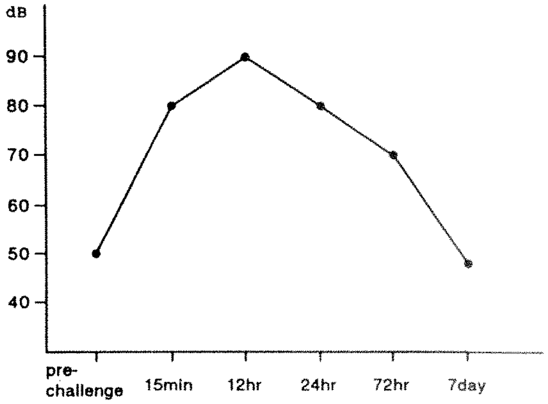

Fig 4. Changes of threshold on auditory brain stem response in 1 of sensitized animals after challenge. Threshold had increased by 15 minutes and had decreased by 24 hours, and finally returned to prechallenge level at 7 days after challenge.

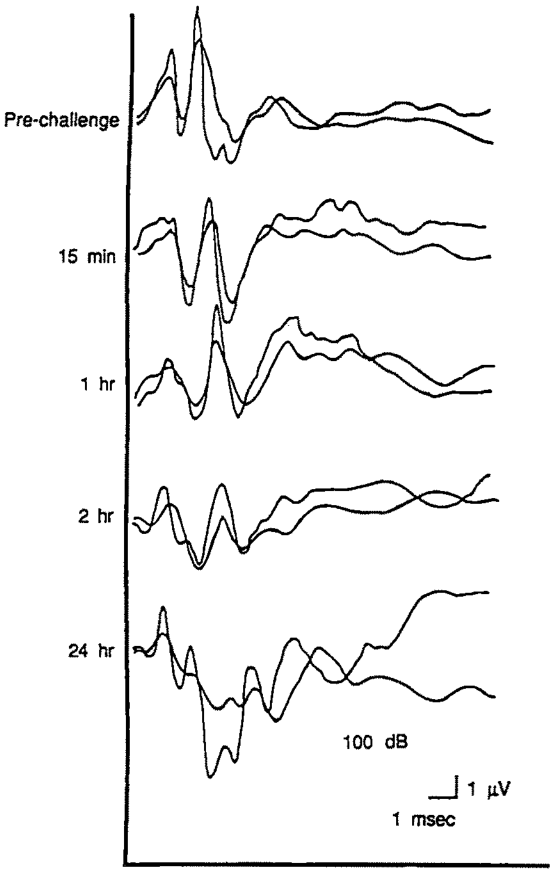

Fig 5. Auditory brain stem response waveforms at 100 dB hearing level before challenge and at 15 minutes, 1 hour, 2 hours, and 24 hours after challenge.

at 2 hours, and −0.2 to 0.1 at 24 hours after the challenge. The increments at 80 dB HL ranged from 0.6 to 0.95 milliseconds at 15 minutes, 0.8 to 1.05 at 1 hour, and 0.55 to 0.65 at 24 hours after the challenge. At 70 dB HL, they ranged from 0.9 to 1.15 milliseconds at 1 hour, and 0.5 to 0.6 milliseconds at 24 hours after the challenge. These changes in ECochG and ABR were not observed in the control group.

Head Deviation. Head deviation and horizontal nystagmus were observed in 20 of 25 animals after local challenge. The nystagmus was directed toward the side opposite the challenged ear, and head deviation was directed toward the challenged side. These changes occurred within 15 minutes and nearly disappeared within 24 hours. Tranilast treatment almost completely inhibited head deviation and nystagmus. Only 3 of 15 Tranilast-treated animals showed slight head deviation, with no detectable nystagmus.

DISCUSSION

In a previous study, Miyamura et al[1] sensitized guinea pigs with sera containing anti-DNP immunoglobulin E (IgE) antibody and specifically challenged the animals with DNP-BSA injected through the stylomastoid foramen. They demonstrated that head deviation, nystagmus, and negative SP on the ECochG were provoked in these animals after specific antigen challenge. These reactions were thought to be IgE-mediated.

In order to investigate and confirm these audiological changes, we performed time-course studies on ECochG and ABR in animals that were sensitized and specifically challenged by Miyamura's method. We observed a negative SP in 8 of 10 sensitized animals and a decrement in whole nerve action potentials in 2 of 10 sensitized animals, while these changes were not observed in control groups. Decrements in whole nerve action potentials were observed 72 hours after the local challenge. In 6 of the 8 animals that showed a negative SP after the challenge, recovery from this change was complete within 72 hours. These reversible auditory changes were also observed on the ABR. Threshold increases were ob-

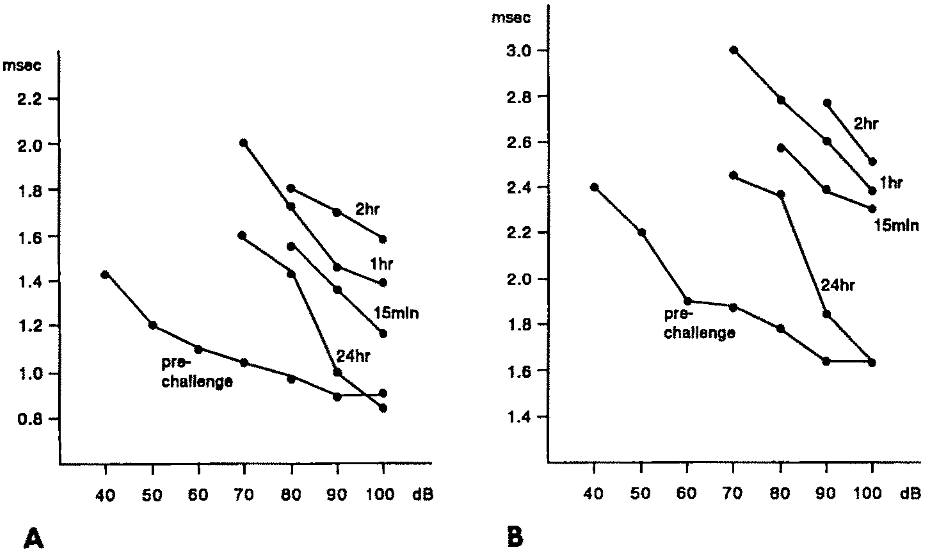

Fig 6. Changes of latency-intensity curves of wave I on auditory brain stem response in 2 sensitized animals. Latencies began to increase shortly after challenge and had decreased by 24 hours. A) One animal. B) Another animal.

served in 4 of 5 sensitized animals 12 hours after the specific challenge; thresholds recovered to pretreatment levels within 7 days, and these changes were not observed in the control group.

Our results for ECochG and ABR were very similar to the auditory features of Meniere's disease in 3 ways. First, the negative SP observed on the ECochG of these experimental animals is also observed in Meniere's disease. Second, the increase of wave I peak latency on the ABR that was observed in the animals is usually observed in the cochlear disturbance of Meniere's disease. Third, these changes in the ECochG and ABR of the animals were reversible, as are such changes in Meniere's disease. On the basis of these points, we may conclude that in our study endolymphatic hydrops was provoked in the reagin-sensitized animals by the specific antigen challenge, and that the hydrops resolved within several days.

Additionally, decrements of whole nerve action potentials were observed in our study. Although the decrements appeared after the restoration of negative SP, this fact may indicate the increment of thresholds of whole nerve action potentials. However, since multiple time-course measurements were performed, we cannot deny the possibility that these decrements may have been caused by differences in the resistance of electrodes at each measurement. In our previous investigation, an allergic reaction mediated by reaginic antibody (probably IgE antibody) was also probably induced in the inner ear of sensitized guinea pigs.[16]

A local anaphylactic reaction requires the presence of mast cells in the inner ear, and also requires entry of antigen into the inner ear. The presence of mast cells in the inner ear has been documented by Rask-Andersen and Stahle,[17] and Kanzaki et al[18] have shown mast cell degranulation after local antigen challenge. Kanzaki et al also observed that carbon particles entered the inner ear when injected through the stylomastoid foramen. Therefore, it can be suggested that the reversible auditory changes provoked after the specific challenge in our experiment were induced by type I allergy.

Furthermore, we were able to inhibit the appearance of negative SP and head deviation after the specific challenge by using an inhibitor of chemical mediator release from mast cells. According to Sakano and Yoshimura,[15] Tranilast suppresses IgE-mediated histamine release but does not suppress spontaneous histamine release. The dose of Tranilast we used in this investigation was considered sufficient to suppress IgE-mediated histamine release. The Tranilast-induced inhibition of negative SP and head deviation may therefore be evidence that the auditory reactions provoked were induced by type I allergy.

Some studies have described the relationship between type I allergy and Meniere's disease. Duke[5] documented 2 patients with Meniere's disease who had food allergies. Proetz,[6] Rowe and Richet,[7] and Balveat[8] also reported some cases of Meniere's disease caused by food sensitivity. Since Yandell[9] first reported a case caused by an inhalant allergen, orris root, in 1933, several patients with sensitivities to inhalant allergens such as orris root, house dust, and molds have been documented, respectively, by Bray,[10] Powers,[11] and Clemis.[12]

The relationship between Meniere's disease and local type I allergic reaction is extremely difficult to prove in humans. However, our experimental results are probable evidence of a close relationship between Meniere's disease and the chemical mediator release from local mast cells that is induced by type I allergy.

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CLINICAL APPLICATIONS OF VESTIBULAR SCIENCE

The conference Clinical Applications of Vestibular Science will be held in Los Angeles, California, February 12-13, 1994. For information, contact Marjorie Harris, Program Coordinator, 15-50 Rehabilitation Center, UCLA, Los Angeles, CA 90024-1651; telephone (310) 825-5131; fax (310) 206-2327.

* * *

EXTRACRANIAL OPTIC NERVE DECOMPRESSION

A meeting to discuss extracranial optic nerve decompression as a treatment for traumatic optic neuropathy will be held November 6-7, 1993, at Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. For information, contact Michael Joseph, MD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114-3096; telephone (617) 573-3192; fax (617) 573-3914.

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ASSOCIATION FOR RESEARCH IN OTOLARYNGOLOGY

The 1994 Midwinter Meeting of the Association for Research in Otolaryngology will be held in St Petersburg Beach, Florida, February 6-10, 1994. For information, contact Michele Johnson, Executive Secretary, 431 E Locust St, Suite 202, Des Moines, IA 50309; telephone (515) 243-1558; fax (515) 243-2049.

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INCOMPLETE COVERAGE OF MAMMALIAN BONE MATRIX BY LINING CELLS

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A functional "membrane" is thought to exist that separates the general extracellular fluid from the bone extracellular fluid. Many investigators have concluded that bone lining cells form this barrier. It is posited that alterations in this barrier may lead to the recruitment of osteoclasts and contribute to the control of extracellular calcium homeostasis. The present ultrastructural studies, however, demonstrated that significant portions of the resting bone are in contact with the general extracellular fluid. In certain regions of the cochlea, up to 88% of the bone surface is in contact with extracellular fluid. These anatomic observations require a critical reevaluation of current theories of the physiologic roles of bone lining cells in osteoclast recruitment and calcium homeostasis.

KEY WORDS — bone lining cells, bone surface, cochlea, osteoclasts.

It is widely accepted that all inactive mammalian bone is covered by a cellular layer termed bone lining cells (BLCs).[1-3] These cells are flattened, with sparse cytoplasm observed near bone surfaces. The definition excludes active osteoblasts and osteoclasts on the bone surface.[2] This cellular covering was first considered to be a membrane by Howard[4] in 1959 and is still considered the anatomic basis for the separation of the bone matrix from the general extracellular fluid (GECF). It is stated that this layer of cells forms a membrane that physically partitions the GECF compartment from a bone extracellular fluid (BECF) compartment,[1,5-8] and that this lining is capable of maintaining concentration differences between the fluid phase of bone and the GECF compartment, thereby controlling calcium exchange and homeostasis by physically partitioning the bone surface from the GECF.[9] It has been hypothesized that under hormonal influences gaps occur between BLCs, allowing the solubilization of calcium from the bone matrix.[2,6,8,10]

It is also suggested that the BLC "membrane" may play an important role in the recruitment of osteoclasts to a local site by exposing the bone matrix to the extracellular fluid (ECF).[11] According to this hypothesis, the matrix of bone is partitioned from the ECF under physiologic conditions. With appropriate stimulation, the BLCs retract and expose "bare" surfaces of bone that initiate a signal for the chemoattraction of osteoclasts and/or their progenitors. Not all experimental evidence has supported the concept of a continuous partition between bone and ECF. Macromolecules such as horseradish peroxidase and thorium dioxide have penetrated into the canalicular lacunar region after intravenous injection.[12-14] Some authors have reported small gaps between lining cells, but others have considered such gaps to be a preparation artifact.[15] Parfitt[16] has suggested that a calcium ion gradient could be maintained by an active pump even if minute gaps existed between lining cells.

Herein we report evidence that a variety of functionally different mammalian bone surfaces are not completely separated from the GECF compartment by a cellular structure that could be considered to be a barrier to the free flow of ions and movement of cells.

MATERIALS AND METHODS

Five outbred Swiss-Webster mice, 3 Sprague-Dawley rats, and 7 Mongolian gerbils *(Meriones unguiculatus)* were used. All animals were adult

BONE LINING CELL SURFACE AT DIFFERENT ANATOMIC SITES IN GERBILS

Site	*BLC/BS (%, mean ± SD; n = 3)*	*Overlying Tissue*
Ulna (endosteal)	100.0	Bone marrow
Ulna (periosteal)	86.8 ± 13.5	Dense fibrous
Calvarium (periosteal)	84.0 ± 10.7	Dense fibrous
Bulla (inner surface)	66.4 ± 16.6	Loose subepithelial
Cochlea (endosteal)	71.1 ± 15.1	Perilymphatic fluid
Cochlea (modiolus)	12.0 ± 6.9	Cerebrospinal fluid
Cochlea (spiral ligament)	60.4 ± 20.5	Loose fibrous

BLC/BS — ratio of bone lining cell surface to bone surface.

From the Department of Otolaryngology, University of California at Davis, Davis, California. Supported by a grant from the National Institutes of Health (RO1 DC00263-06). This study was performed in accordance with the PHS Policy on Humane Care and Use of Laboratory Animals, the NIH *Guide for the Care and Use of Laboratory Animals*, and the Animal Welfare Act (7 U.S.C. et seq.); the animal use protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the University of California at Davis.

REPRINTS — Richard A. Chole, MD, PhD, Otology Research Laboratory, 1159 Surge III, University of California at Davis, Davis, CA 95616.

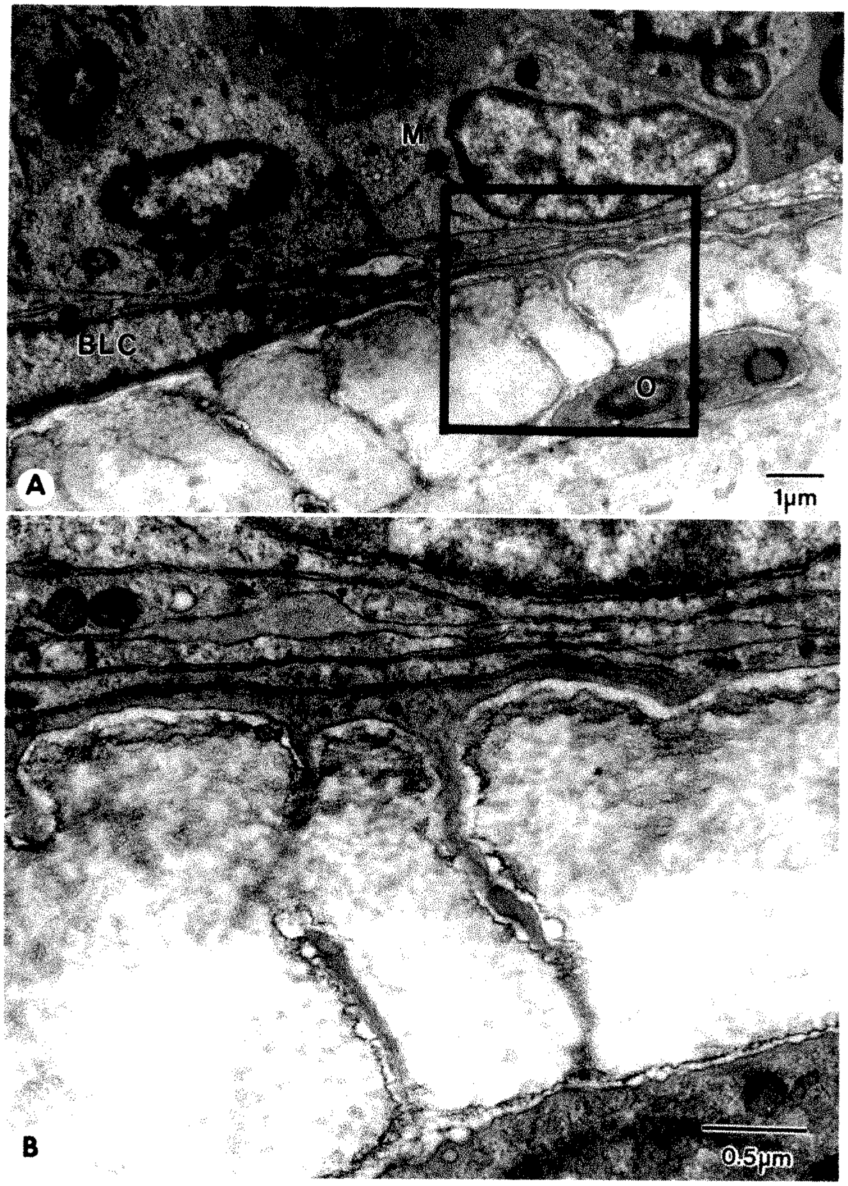


Fig 1. A) Transmission electron micrograph of bone lining cells (BLC) of marrow cavity (M) covering surface of osteoid layer in gerbil radius. B) Higher-magnification view of endothelial cell-to-cell interface boxed in A. Note lack of gaps between adjacent BLC, close approximation of cells to bone, and lack of shrinkage of BLC or osteocyte (O).

males between 110 and 150 days of age. Under deep pentobarbital sodium anesthesia, each animal was perfused with a 0.9% sodium chloride solution for 1 minute followed by a fixative. To compare effects of fixation, some animals were fixed with 10% phosphate-buffered formalin, pH 7.4, and others with a solution of 2% glutaraldehyde, 2% paraformaldehyde in 0.08 mol/L cacodylate at pH 7.4. Tissues were then prepared for scanning electron microscopy (SEM) and transmission electron microscopy (TEM). Some of those prepared for TEM were decalcified, others were not. Tissues subjected to decalcification were decalcified in 0.1 mol/L ethylenediaminetetraacetic acid in a 2% glutaraldehyde, 2% paraformaldehyde solution buffered to pH 7.4 with 0.08 mol/L cacodylate buffer. Tissues for TEM were post-fixed in 2% osmium tetroxide in cacodylate buffer at pH 7.4, dehydrated in graded acetone, and embedded in an Epon-araldite mixture. Tissue samples from the long bones, rib, calvarium, cochlea, and middle ear were harvested as atraumatically as possible. Some tissue samples with exposed surface layers (long bone endosteum and cochlea) were fresh frozen in acetone at −110°C, then lyophilized in a Freezemobile 12 (Virtis Co, Gardiner, NY) for SEM preparation.

Quantitative measurements were performed on gerbil tissues. Lining cells within 5 µm of the bone surface were measured; the margin of each lining cell was defined by a line perpendicular to the bone surface, and gaps between these lines were measured. No gap would be counted if 2 adjacent lining cells overlapped, even if they were not attached by junctional complexes. For purposes of quantitation, sections were randomly selected from the designated bone surfaces and the entire section was measured. Each sample consisted of at least 3 mm (linear) of

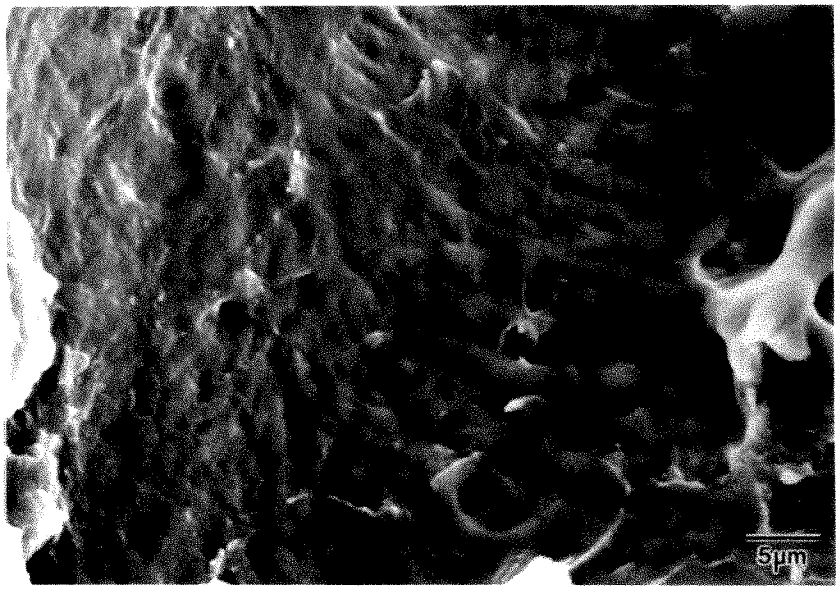


Fig 2. Scanning electron micrograph of long bone endosteum fresh frozen and lyophilized after marrow was washed out mechanically. Note absence of gaps or shrinkage artifact.

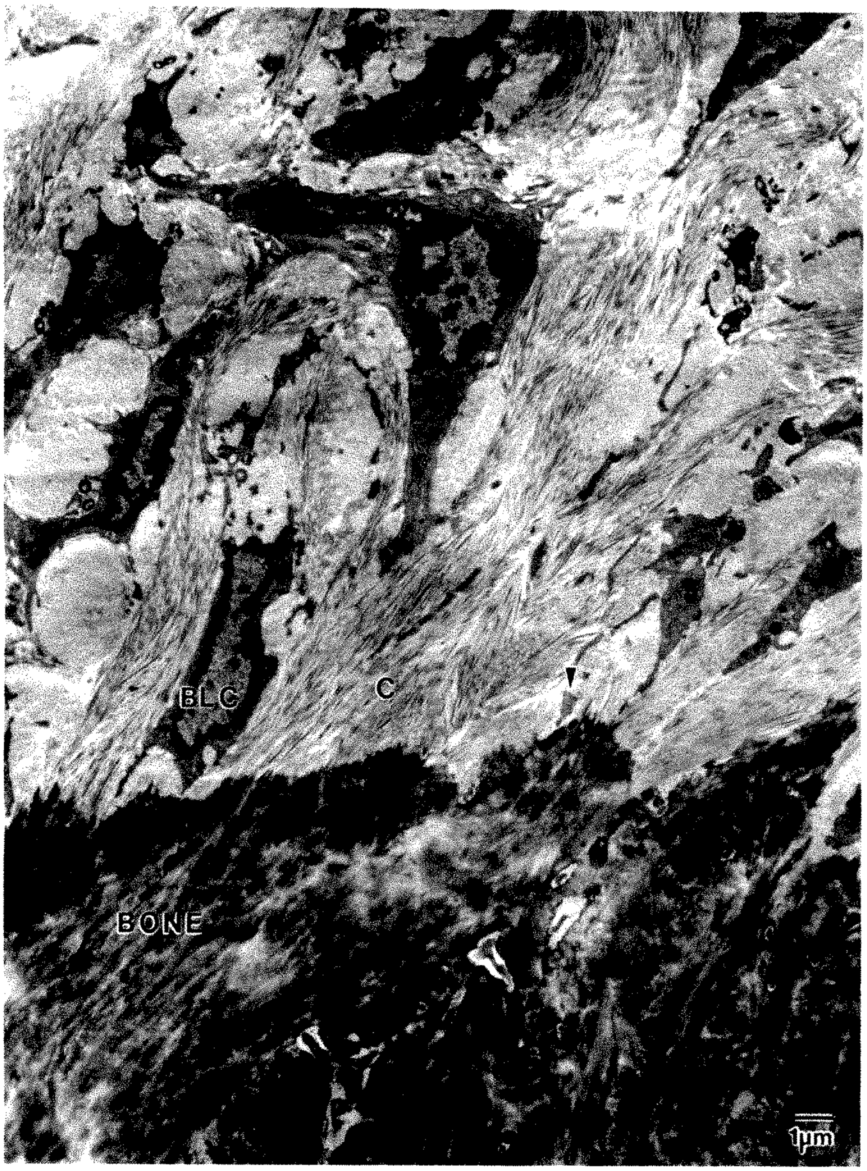


Fig 3. Transmission electron micrograph of periosteal surface of gerbil radius (decalcified). Bundles of collagen (C) can be seen within gaps between bone surface and overlying bone lining cells (BLC and arrowhead), adding further evidence that spaces are not artifactual.

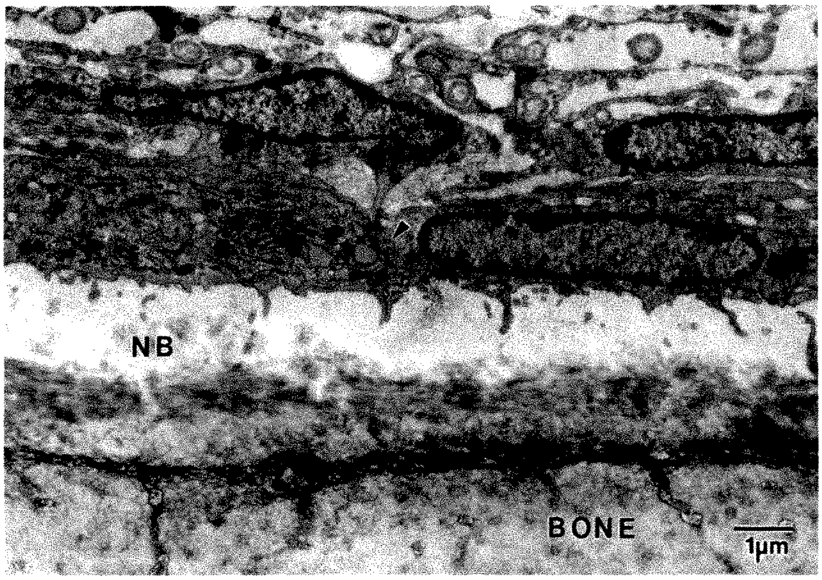


Fig 4. Transmission electron micrograph of periosteal surface of gerbil radius in area of new bone (NB) formations (decalcified). Note close interdigitation of adjoining osteoblasts (arrowhead).

bone surface.

RESULTS

Putative BLCs were found in the vicinity of all quiescent bone surfaces. The endosteal surface of long bones appeared to have a continuous cell lining with gap junctions (macula communicans), whereas under identical fixation and preparation conditions, other sites had large gaps (see Table). The lining cells appeared to be most sparsely distributed in the region of the endosteal surface of the cochlea and modiolus. No qualitative histologic differences were seen among rats, mice, and gerbils.

The endosteal surfaces of long bones were covered by a continuous layer of cells with overlapping areas connected with gap junctions (macula communicans); no gaps were observed (ratio of BLC surface to bone surface [BLC/BS] was 100%; Fig 1). These lining cells appeared to form a continuous layer when observed by TEM after fixation with mixed aldehydes and post-fixation with osmium tetroxide, or when rapidly fresh frozen (Fig 2). In undecalcified specimens, the lining cells appeared to cover a 0.5- to 2.0-μm-thick, nonmineralized bone matrix on the surface of the bone.

The periosteal surface of long bones was not covered by a continuous layer of BLCs (Figs 3 and 4). Discontinuity between cells was frequent. Bundles of collagen were often seen within these gaps. The BLC/BS was 86.8% ± 13.5%. Gaps between cells were found regardless of the fixation technique used.

The bony wall of the middle ear (bulla) revealed larger areas of bone matrix exposed to GECF (Fig 5); the BLC/BS was 66.4% ± 16.6%. Undecalcified specimens prepared for TEM confirmed the findings

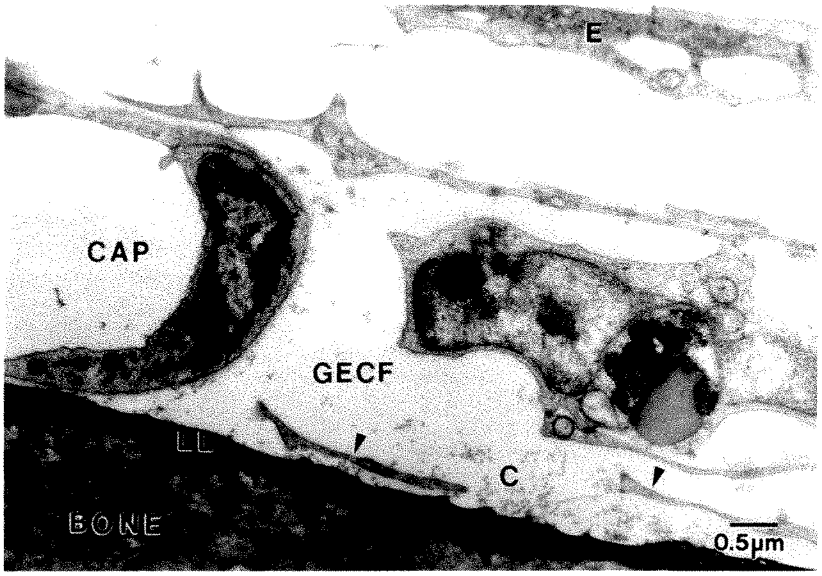


Fig 5. Transmission electron micrograph of decalcified bulla wall and overlying epithelium (E). Darkly staining lamina limitans (LL) of bone surface is exposed directly to general extracellular fluid (GECF) through gaps in sparsely distributed bone lining cells (arrowheads). There are no bone lining cells between capillary (CAP) and bone matrix. C — collagen.

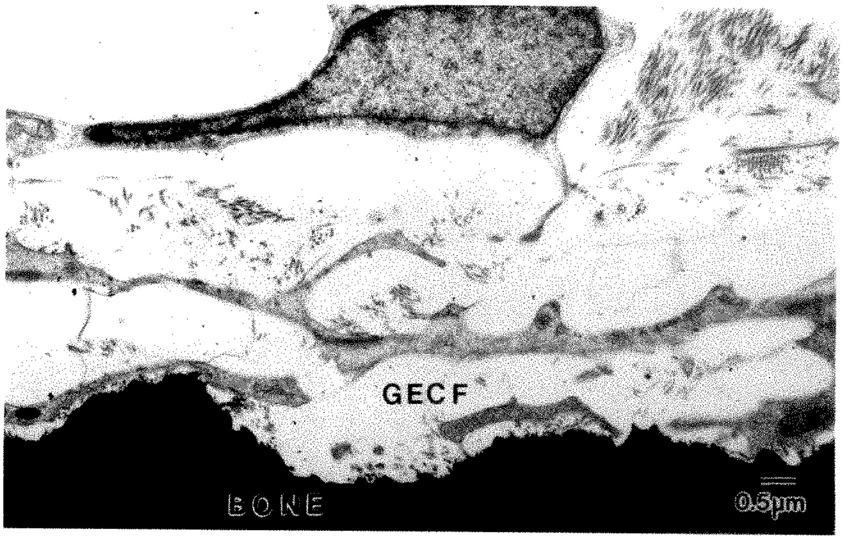


Fig 6. Transmission electron micrograph of undecalcified bulla wall. Electron-dense, calcified bone matrix includes lamina limitans and is in contact with general extracellular fluid (GECF).

of the decalcified material. Bone surfaces of the bullae were not always covered by noncalcified matrix. Heavily calcified bone matrix, corresponding to the lamina limitans, appeared to be in direct contact with the GECF (Fig 6). These surfaces were not available for SEM study because of the overlying epithelial cells.

Ultrastructural studies of the endosteal surface of the cochlea and modiolus revealed a more sparse population of BLCs (Fig 7). In some regions, there were wide discontinuities between lining cells as revealed by SEM and TEM in decalcified and undecalcified specimens. Within the scala tympani of the cochlea, BLCs could be seen directly with SEM, since no endothelial covering is present (Fig 8). The BLC/BS was 71.1% ± 15.1%.

Bone lining cells were also sparse beneath the spiral ligament of the cochlea (Fig 9). The BLC/BS was 60.4% ± 20.5%. In this anatomic region large areas of bone surface are directly bathed in GECF, even in areas subjacent to capillaries. The modiolus (Fig 7), which contains the terminal portion of the auditory nerve, also had few lining cells (BLC/BS of 12.0% ± 6.9%).

DISCUSSION

There is evidence that the BECF compartment may be functionally separated from the GECF compartment.[17-19] The potassium concentration was found to be higher in BECF than in GECF,[17,18] and the solubility of bone calcium is dependent on a potential difference between bone and ECF.[19] Support for the concept of an active partition between the GECF and BECF compartments was shown with secondary ion mass spectroscopy[20]; live bone had more potassium and sodium relative to calcium than did dead bone. There was a fall in the potassium-calcium ratio and an increase in the sodium-potassium ratio with death; thus, it appears as though bone mineral is maintained in physicochemical equilibrium by active biologic processes. Many investigators have concluded this barrier is made up of a cellular lining on all bone surfaces that anatomically isolates bone from the GECF.[1,5-8,12,15,21-24] Previous anatomic evidence for the concept of a BLC "membrane" is principally based on the ultrastructural study of the endosteal surface of long bone. In the present study no anatomic gaps were observed between BLCs of long bone marrow cavities; zonula communicans could often be seen between adjacent cells. Miller et al[25] have shown discontinuities in this cellular layer, but they have concluded that these gaps were either artifactual or did not represent significant communications with the GECF.[12] However, if the BLCs indeed serve to separate the BECF from the GECF in order to maintain the physicochemical equilibrium, one would anticipate that all bone surfaces, regardless of anatomic location, would be covered by such a "membrane."

In the results of this study, we found no evidence for a general, continuous, membranelike barrier between the BECF and the GECF. On the contrary, mammalian bone in several anatomic locations is not covered by continuous lining cells. The discontinuities observed in this study are far too great to be explained by artifactual changes. Although differential shrinkage may have accentuated spaces between cells, large regions of bone exposed to the ECF of the scala tympani and beneath the spiral ligament cannot be explained on the basis of artifact, because the same results were seen on both TEM and SEM with several different preparation techniques, with and without decalcification. Findings of gaps between cells may represent artifacts due to differential shrinkage of

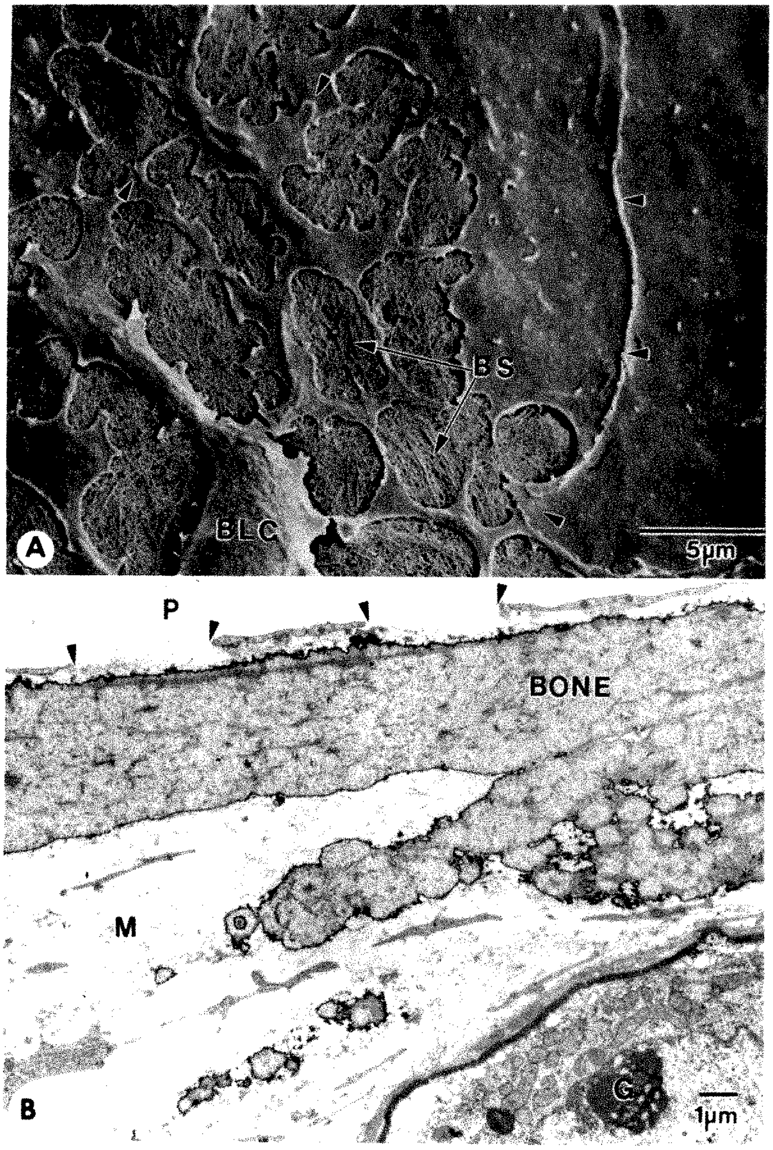
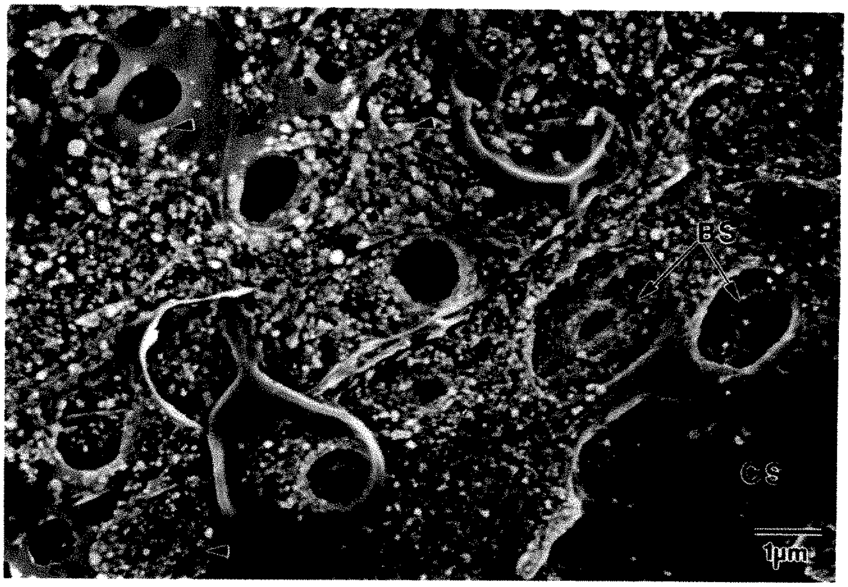


Fig 7. A) Representative scanning electron micrograph of bone lining cells (BLC) covering wall of scala tympani in gerbil cochlea. Large areas of calcified bone surface (BS) are directly exposed to perilymph in extracellular fluid compartment. Note some adjacent tightly apposed and overlapping cell-to-cell contact regions (arrowheads). B) Transmission electron micrograph corresponding to perpendicular section through A. Gaps in BLC (arrowheads) expose wall of scala tympani to perilymph (P). Major portion of BS within modiolus (M) is not covered by BLC and is bathed in general extracellular fluid. Ganglion cells (G) often directly appose bone within M.

Fig 8. Scanning electron micrograph of surface of scala tympani, fresh frozen and lyophilized. Note large gaps exposing bone surface (BS) and tightly apposed cell-to-cell interface (arrow). Some cell surfaces (CS) are obscured by precipitated salts (arrowheads) from lyophilized perilymph, which are not present in perfusion-fixed material (see Fig 7A). Compare this image to similarly prepared marrow endosteum depicted in Fig 2.



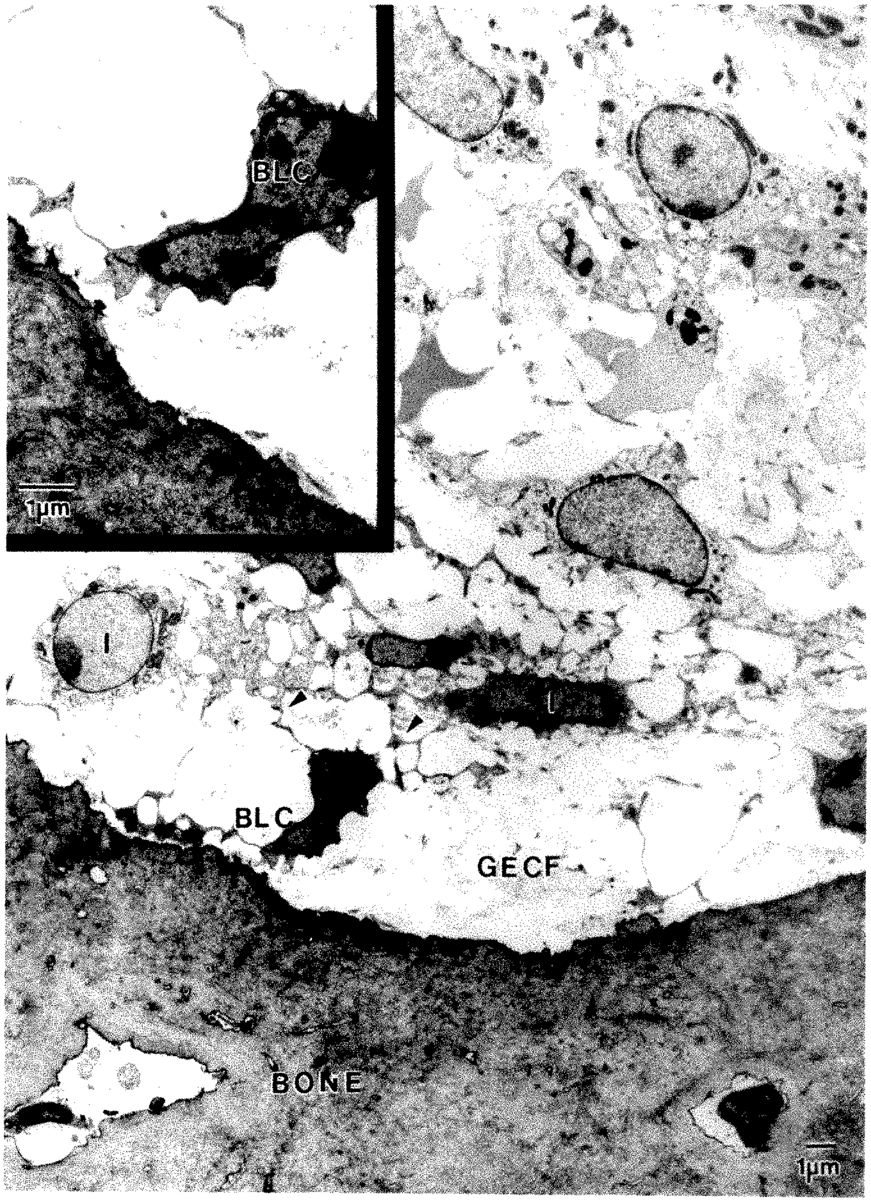


Fig 9. Transmission electron micrograph of spiral ligament of cochlea. Interstitial cells (I) are widely dispersed, with long processes joined by junctional complexes (arrowheads). Bone lacks continuous covering of bone lining cells (BLC) and is bathed in general extracellular fluid (GECF). Inset) Higher-magnification view of bone-BLC interface pictured below.

bone versus lining cells; however, in the present study identical preparation techniques resulted in the appearance of a continuous lining within long bones and large discontinuities in some other sites. Furthermore, when we prepared tissues by flash freezing, gaps were still visible. It is likely that differential shrinkage of tissue types exaggerated the gap in some specimens, but the lack of gaps in long bone endosteum and the presence of gaps in several other tissues support the contention that the gaps are real. The endosteal surface of the scala tympani is bathed by perilymph, which is an ECF that is similar but not identical to cerebrospinal fluid[26]; this may represent a unique anatomic relationship. This unique relationship notwithstanding, the presence of discontinuities in lining cells beneath the spiral ligament of the cochlea, the periosteum of the middle ear bone, and periosteal surfaces of long bones leads us to conclude that the surface of bone matrix is commonly exposed to GECF and that BLCs cannot be considered a universal barrier between the BECF and the GECF.

These anatomic findings require the reevaluation of 2 widely held hypotheses. First, the concept that lining cells prevent the initiation of osteoclastic resorption has been hypothesized[7] and supported by the in vivo studies of Zallone et al.[27] This hypothesis is not consistent with our data herein presented. Second, the hypothesis that a lining cell "membrane" plays a role in calcium hemostasis by intermittently exposing bone matrix to GECF appears inconsistent.

The biophysical characteristics of the lamina limitans[28] may represent the "bone membrane"[17,18] and may play a significant role in the maintenance of the integrity of bone surfaces and calcium flux. It is possible that BLCs may directly maintain the lamina limitans and may be the site of the local control of the remodeling process,[29] but they do not do so by universally sequestering the bone from the GECF.

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EFFECT OF INFLUENZA A VIRUS ON CILIARY ACTIVITY AND DYE TRANSPORT FUNCTION IN THE CHINCHILLA EUSTACHIAN TUBE

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Previous studies have shown that influenza A virus inoculated via a transbullar approach can cause severe disorders of the chinchilla eustachian tube. In this study, we inoculated chinchillas both intranasally and transbullarly with influenza A virus (A/Alaska/6/77) to assess the effect of this virus on both the ciliary activity of eustachian tube epithelium and eustachian tube transport function. Data indicated that while the nature of the major lesions was indistinguishable, the differing routes of inoculation did influence the time course and initial location of virus-induced histopathology. Analysis of ciliary beat frequency and dye transport function indicated a maximal decrease approximately 7 to 14 days postinoculation, with return to normal function by 28 days postinoculation. Light and transmission electron microscopic observations of the evolution of histopathology and return to normal histology correlated well with functional assessment data.

KEY WORDS — eustachian tube ciliary function, influenza A virus.

INTRODUCTION

Epidemiologic data have long indicated that upper respiratory tract infection with influenza A virus infection often precedes a peak incidence of otitis media (OM).[1-3] The mechanisms by which this predisposition occurs are not fully understood, although it is known that influenza A virus induces abnormal ciliary morphology,[4] polymorphonuclear neutrophil (PMN) dysfunction,[5,6] negative middle ear pressure,[7] and eustachian tube (ET) histopathology.[8,9] In addition, influenza A virus infection of various respiratory epithelia is known to alter the adherence of various pathogens,[10-14] and respiratory tract viruses have been shown to interfere with the bacteriologic response to antibiotics.[15] Data from our laboratory, following transbullar inoculation of chinchillas with influenza A virus, have indicated that maximal histopathology, with notable severe inflammation and damage to cilia or ciliated cells, was achieved 2 days after inoculation of virus, with full recovery to normal histology occurring approximately 28 days postinoculation.[9,16] In this study, we were interested in assessing the effect that this virus had on ciliary activity within the ET as measured by both a quantitative motion analysis system[17] and an in situ dye transport assay[18] that measures one aspect of ET function that is intimately associated with ciliary activity. Because our previous data[9,16] were obtained by transbullar challenge, this route of inoculation was maintained in the present study; however, we also used an intranasal inoculation route for comparison, as this more closely mimics the natural route of human acquisition of this pathogen. An assessment of whether or not the route of inoculation used affected the location or severity of the induced histopathology within the ET, as well as the functional correlates, is presented.

MATERIALS AND METHODS

Animals. A total of 67 healthy adult chinchillas *(Chinchilla laniger)*, free of middle ear disease as determined by otoscopy, was used for all experiments. This animal was chosen because of its widely accepted use as an experimental model of human middle ear disease.

Agent. Influenza A/Alaska/6/77 (H3N2) virus, passaged on Madin-Darby canine kidney (MDCK4) cells to produce a working virus pool, was titered by plaque formation on this cell line. Appropriate dilutions were made in Eagle's minimum essential medium (MEM; MA Bioproducts, Walkersville, Md), and 2 cohorts of chinchillas (n = 16 per cohort) were

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inoculated either transbullarly (bilaterally) with 0.3 mL as previously described[9] or intranasally with 0.5 mL (inoculum divided between nares) to deliver approximately 6 x 10^6 plaque-forming units of virus. Two animals were sacrificed on each of days 1, 2, 4, 7, 10, 14, 21, and 28 postinoculation by a lethal dose of ketamine and xylazine administered intramuscularly. Control animals (n = 12) received sterile MEM via either an intranasal or a transbullar route and were assessed at identical time points within the 28-day observation period.

Otoscopy. Animals were examined daily by otoscopy, and all signs of tympanic membrane (TM) abnormality were noted. On the day they were sacrificed, tympanocentesis was performed through the left TM only (n = 16 per cohort), and gentle negative pressure was applied to aspirate any middle ear fluid (MEF) present. The color, volume, turbidity, and viscosity of any recovered fluids were noted. All tapped bullae were then subjected to lavage with 0.5 mL of prewarmed sterile normal saline. Lavage fluids were added to any recovered MEF and used for preparation of differential counts and bacterial and viral cultures.

Cytology. For cytology, a 50-μL aliquot of the combined MEF and lavage fluid was cytocentrifuged (Shandon, Pittsburgh, Pa) as previously described.[19] The slide was then air-dried, fixed, and stained with Wright's stain for evaluation of number and types of inflammatory cells. One hundred cells were counted at random.

Bacterial Culture. Bacterial cultures were prepared by spreading 0.1 mL of the combined MEF and lavage fluids on a 5% sheep blood agar plate and incubating at 37°C in a humidified atmosphere of 5% carbon dioxide for up to 72 hours to rule out a bacterial component to any noted pathologic changes.

Viral Culture. Viral culture was performed by the Cell Culture Service at The Ohio State University Hospitals. A 0.35-mL aliquot of the combined MEF and lavage fluid was added to viral transport medium (Hank's balanced salt solution with 25 mmol/L HEPES; 50 U of penicillin per milliliter; 50 μg of gentamicin per milliliter; 2.5 U of amphotericin B per milliliter; and lactalbumin 0.5%) and kept on ice. Aliquots were assessed for presence of virus by characteristic cytopathic effect on MDCK4 cells and demonstration of hemadsorption. Viral preparations were quantitated by plaque assay on MDCK4 cells.

Nasopharyngeal Lavage. After collection of any MEFs and bulla lavage fluids, a nasopharyngeal (NP) lavage (n = 16 per cohort) was performed by slow instillation of 1.0 mL of sterile normal saline into the uppermost naris of the chinchilla while it was lying on its side, while the opposite naris was intubated and gentle negative pressure was applied until 0.5 mL of lavage fluid was collected. The lavage fluids were then added to 0.5 mL of viral transport medium on ice and taken to the Cell Culture Service within 2 to 3 hours of collection for assessment of the presence and titer of influenza A virus.

Assessment of Ciliary Activity. The ETs obtained from the right side of all virus-inoculated animals (n = 16 per cohort) were prepared for ciliary motility analysis after decapitation. The ETs were dissected into ice-cold MEM with HEPES buffer (MA Bioproducts). A longitudinal incision was made to expose the cartilage, and the mucosa was elevated into the cold medium. The tissue was divided into pharyngeal and midtympanic portions and placed in fresh cold medium. A Dvorak-Stotler Chamber (Nicholson-Precision Instruments Inc, Gaithersburg, Md) was prepared by filling with warm MEM (supplemented with 50 U penicillin and 5 μg streptomycin per milliliter (MEM-PS; Gibco, Grand Island, NY). The ET sections were then placed in the center of the chamber, positioned on a heated microscope stage, and perfused with prewarmed MEM-PS. Readings of ciliary activity were obtained by a modified version of the photoelectric diode technique of Gabridge.[17] Five readings of ciliary beat frequency (CBF, in hertz) were obtained for each of 3 tissue pieces from both tympanic and pharyngeal portions of all ETs.

Assessment of Dye Transport. Dye transport function was assessed on a separate cohort of chinchillas (n = 24 control ears; n = 14 virus-inoculated ears) inoculated transbullarly with an identical inoculum by the method of Bakaletz et al.[18] Briefly, anesthetized animals were prepared for dye transport assay by surgical incision of the soft palate to visualize the pharyngeal orifices of the ETs. A small volume (0.15 mL) of 5.0% Coomassie brilliant blue was injected into the superior bullae of the test animals, and the time (seconds) required for the dye to just become visible at the pharyngeal orifice of the ET was recorded.

Light and Electron Microscopy. The ET from the left side of each animal at each time point was prepared for light microscopy (LM; n = 8 per cohort) or for transmission electron microscopy (TEM; n = 8 per cohort). For LM, 3.0 cc of Z-fixative (Anatech Ltd, Battle Creek, Mich) was injected into the bulla, and the temporal bone was removed and immersed into the same fixative. The temporal bones were decalcified in 10% ethylenediaminetetraacetic acid in 0.1 mol/L Tris-buffered saline. The specimen was then dehydrated by passage through a graded series of ethanol, embedded in JB-4 resin (glycomethacrylate; Polyscience, Warrington, Pa), and divided into tympanic and pharyngeal portions for sectioning. Sections were stained with hematoxylin and eosin for routine histologic examination. The remaining ET was prepared by injection of 2% glutaraldehyde into the superior bulla. The temporal bone was removed, immersed in the same fixative, decalcified with 5% ethylenediaminetetraacetic acid, and later post-fixed in 1% osmic acid for 1 to 2 hours. After dehydration in ethanol, tissues were embedded in Epon, sectioned, and stained for TEM by standard techniques.

Statistics. All values were assumed to be normally distributed. The arithmetic mean and standard deviation were calculated, and Student's *t* test was used to determine differences among means. A p value less than or equal to .01 was selected as the minimum level of significance for all studies.

RESULTS

Otoscopic and Culture Findings. Despite overall mild TM pathology, animals receiving a transbullar inoculation of influenza A virus revealed more frequent pathologic changes than did those animals inoculated intranasally. The typical observation was evidence of mild vascular injection (10 of 32 ears or 31%) and a possible low-volume middle ear effusion (5 of 32 ears or 16%), except for 2 animals in which 1 TM was perforated and the ear discharging at 14 and 21 days postinoculation. Tympanocentesis yielded serous fluid in 3 of 16 tapped ears (19%), while marked hemorrhagic changes of the bullar mucosa were observed in 25 of 32 ears (78%) at dissection as early as 1 day postinjection. Attempts to isolate bacteria from bulla washes yielded only occasional low levels of mixed contaminants, except for the animals with a TM perforation. Examination of cytocentrifuged bulla wash fluid samples showed many PMNs 1 and 2 days postinoculation that evolved to a mild to moderate mononuclear infiltrate at 7 days and continued until approximately 14 days. Attempts to culture virus from NP or bulla wash fluids yielded positive results in 6 of 16 nasal lavage fluids (38%) and 2 of 16 bulla wash specimens (13%). All positive viral cultures occurred within the first 7 days postinoculation (6 of 8 ears or 75% and 2 of 8 bullae or 25%).

For animals receiving an intranasal inoculation of influenza A virus, no notable TM disorder (22 of 32 ears or 69%) was seen via otoscopy for up to 28 days after inoculation, with the exception of evidence of mild injection of vessels (6 of 32 ears or 19%) and possible fluid in the tubotympanum seen occasionally (6 of 32 ears or 19%) after 10 days. Tympanocentesis yielded minimal serous fluid in 2 of 16 tapped ears (13%), while gross observation of the bullar mucosa at dissection of the ETs revealed hemorrhagic conditions in 24 of 32 ears (75%), beginning at 2 days postinjection. Culture of bulla wash fluids again yielded only occasional low-level mixed contaminants, and examination of differentially stained cells from cytocentrifuged bulla wash revealed either no cells (12 of 16 ears or 75%) or a minimal mononuclear cell infiltrate (4 of 16 ears or 25%). Attempts to culture virus on MDCK4 cells from bulla or NP lavage fluids yielded positive results in NP specimens from 2 of 16 animals (13%) at 2 and 4 days postinoculation and in no bulla wash fluids, despite obvious gross pathologic changes that were noted at dissection in 75% of ears. Both positive viral cultures occurred within the first 4 days postinoculation (2 of 6 ears or 33%).

Ciliary Activity. To establish baseline values for CBF at both the tympanic and pharyngeal sites of the chinchilla ET, both normal (n = 3) and sterile medium–inoculated control animals (n = 12) were assessed. The average CBF was 19.2 (± 0.2) Hz for the tympanic portion and 19.3 (± 0.1) Hz at the pharyngeal portion of the normal ET. Those animals receiving sterile MEM by the transbullar route demonstrated an average CBF value of 19.1 (±0.1) Hz at the tympanic portion and 19.2 (±0.04) Hz at the pharyngeal portion of the ET from 1 to 28 days postinoculation. Animals receiving sterile MEM via an intranasal route demonstrated CBF values of 19.1 (±0.1) Hz at the tympanic site and 19.0 (±0.1) Hz at the pharyngeal site from 1 to 21 days postinoculation. There were no significant differences between CBF values at either ET site over time for normal versus sterile medium–inoculated controls.

Animals inoculated transbullarly with influenza A virus demonstrated CBF values that were significantly reduced ($p \leq .01$) from those of controls at equivalent times postinoculation on days 2 through 14 at the tympanic site and on day 2 and days 7 through 14 at the pharyngeal site. Maximal diminution of CBF occurred in both the tympanic (mean 15.9 ± 0.3 Hz) and pharyngeal (mean 18.3 ± 0.1 Hz) portions of the ET 7 days postinoculation. Recovery of CBF levels to baseline occurred at approximately 21 days postinoculation at both sites (Fig 1A). The CBF values of animals receiving an intranasal inoculation of influenza A virus are represented in Fig 1B. The CBF values were significantly reduced ($p \leq .01$) from those of controls at equivalent duration postinoculation on days 1, 4, 10, and 21 and days 1, 4, and 10 for the tympanic and pharyngeal portions of the ET, respectively. The CBF values were not obtained

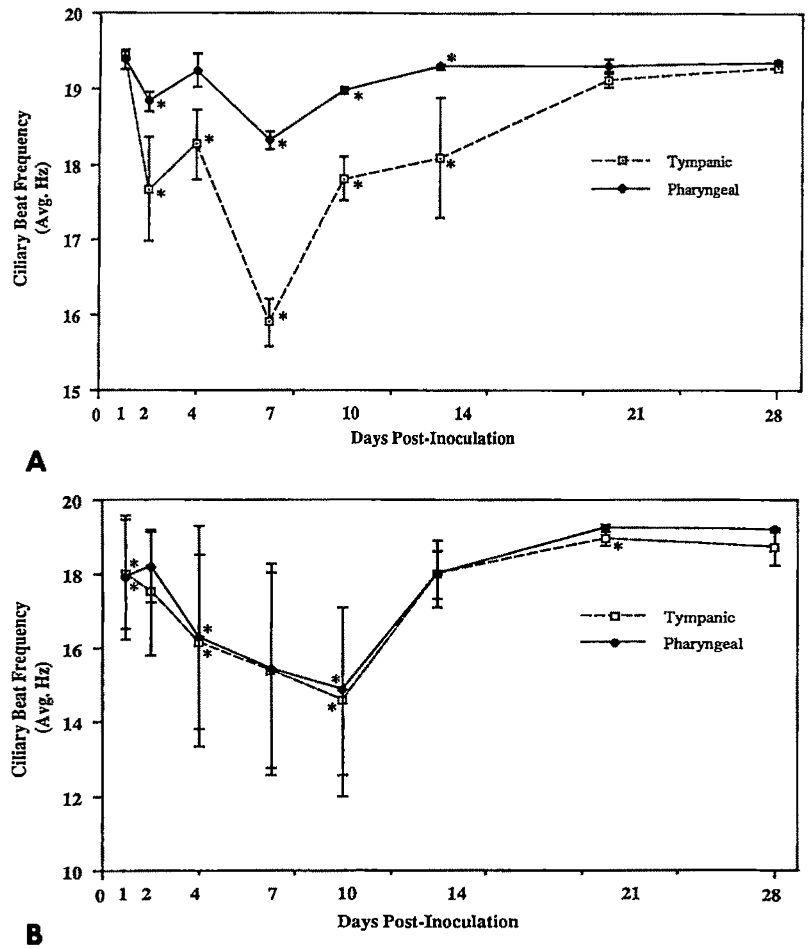

Fig 1. Ciliary beat frequency of chinchilla eustachian tube epithelium at sites near the tympanic or pharyngeal orifice following inoculation of influenza A virus. Asterisk — significant difference (p ≤ .01) from control. A) Transbullar inoculation. B) Intranasal inoculation.

for days 2, 7, 14, and 28 for this control group; however, extrapolation of data or comparison to transbullarly inoculated controls, which were never significantly different from intranasally inoculated controls at any time point, indicates a significant reduction of CBF on the additional days 2, 7, 14, and 28 for the tympanic site and days 2, 7, and 14 for the pharyngeal site. Maximal inhibition of ciliary activity for animals inoculated intranasally occurred at 10 days post-inoculation for both the tympanic (mean 14.6 ± 2.6 Hz) and pharyngeal (mean 14.8 ± 2.3 Hz) portions of the ET. The CBF values returned to normal (19.2 ± 0.1 Hz) at the pharyngeal site approximately 21 days postinoculation.

Dye Transport Function. Dye transport assessment of tubal function was performed on a separate cohort of transbullarly inoculated animals and indicated a significantly delayed transport (p ≤ .01) 24 hours post–virus inoculation that was maintained throughout 21 days of the observation period (see Table). The maximal depression of activity occurred on days 7 and 14. The transport function returned to normal by day 28.

Microscopy Observations. Neither NP lavage nor tympanocentesis resulted in an abnormal appearance of the ET mucosal epithelium in control animals. However, LM demonstrated a disorganized epithelium and the presence of cellular debris in the ET lumen within 24 hours of transbullar viral inoculation (Fig 2A). This histopathology was more prominent in the tympanic portion than the pharyngeal portion of

DYE TRANSPORT VALUES FOR CHINCHILLAS INJECTED TRANSBULLARLY WITH INFLUENZA A/ALASKA/6/77

Days Post-inoculation	*Dye Transport Rate in Seconds (mean ± SD)*			
	Control Ear		*Test Ear*	
1	180 ± 27	(4)	459 ± 31*	(2)
2	130 ± 40	(3)	636 ± 142*	(2)
4	151 ± 29	(4)	670 ± 325*	(2)
7	160 ± 55	(4)	900 ± 0*†	(2)
14	134 ± 31	(4)	900 ± 0*†	(2)
21	139 ± 27	(4)	655 ± 346*	(2)
28	155	(1)	147 ± 23	(2)

Values in parentheses are numbers of ears.
*Significant difference from control (p ≤ .01).
†Fifteen minutes (900 seconds) was arbitrarily selected as upper limit for these studies. No appearance of dye at nasopharyngeal orifice within 15 minutes yielded transport value of 900.

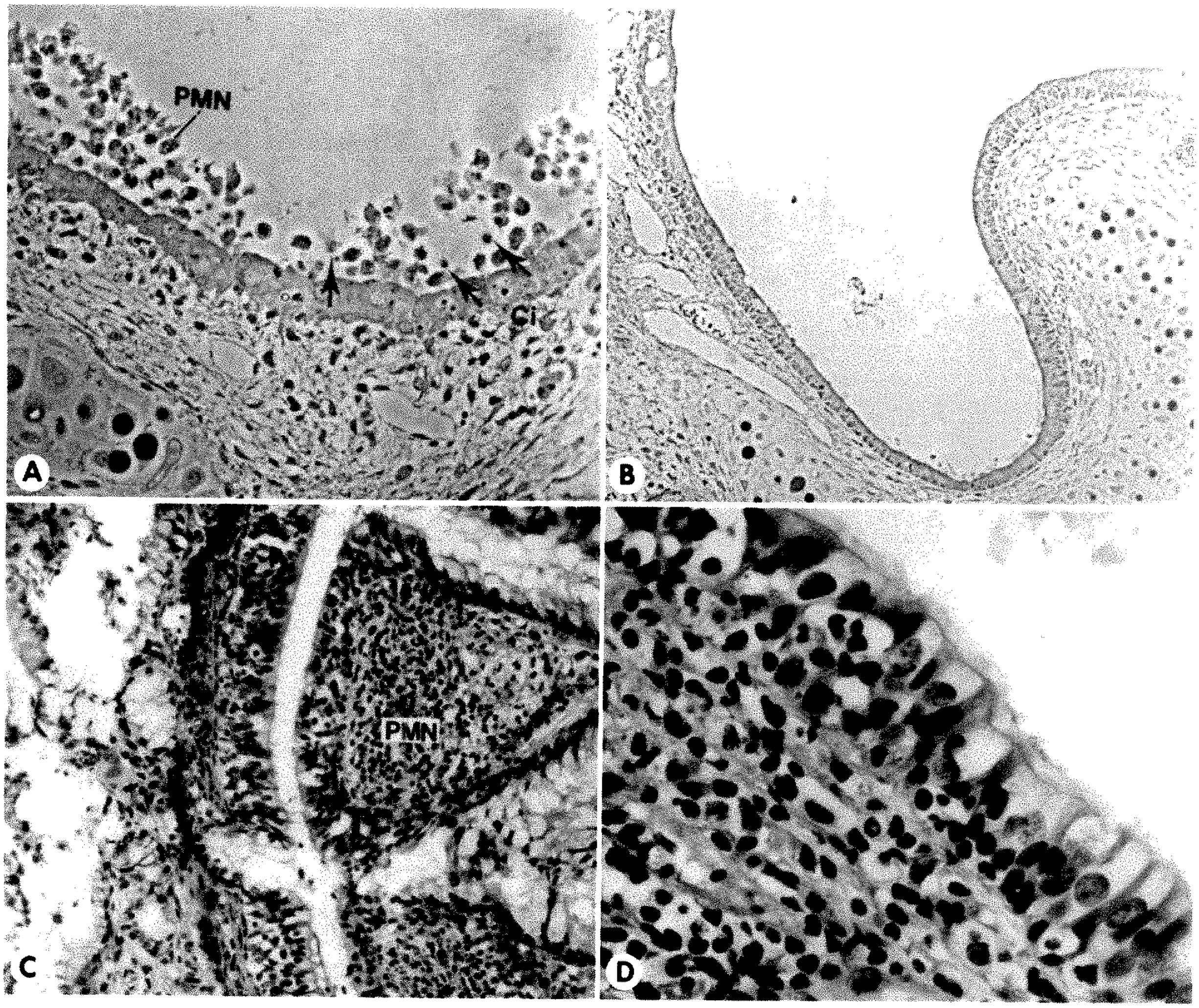

Fig 2. Light micrographs of chinchilla eustachian tube epithelium after transbullar inoculation of influenza A virus. A) One day postinoculation (original x40). Note exfoliated ciliated cells (Ci) at arrows and presence of polymorphonuclear neutrophils (PMN) in lumen. B) At 4 days (original x20). Note focal loss of ciliated cells. C) At 14 days, pharyngeal site (original x20). Note subepithelial infiltration of PMN. D) At 21 days, pharyngeal site (original x64). Note return of ciliated cells despite remaining PMN infiltration.

the ET. The presence of abnormal cilia and focal loss of ciliated cells was observed until 7 days postinoculation (Fig 2B). There was evidence of extensive inflammation with an accumulation of a cellular infiltrate in the subepithelial space in 14-day specimens (Fig 2C). Tissue sections obtained at 21 days demonstrated similar histopathology, although the percentage of ciliated cells and the length of each individual cilium had increased (Fig 2D). By 28 days, the epithelium appeared predominantly normal at both the tympanic and pharyngeal sites. The TEM findings corroborated those of LM (Fig 3).

Light microscopy demonstrated fairly normal histology with some cellular debris in the ET lumen for up to 2 days after intranasal inoculation of virus at both the pharyngeal and tympanic sites (Fig 4A). By 4 days postinoculation, there were obvious pathologic findings in the cilia and focal loss of ciliated cells. Such findings persisted through day 7 (Fig 4B). At 10 days, numerous short regenerating cilia were observed on the epithelial surface (Fig 4C). The regeneration process continued, with obvious lengthening of the ciliary shaft, until day 21, when the epithelium appeared grossly normal, even though a few mononuclear cells were present. At 28 days, the epithelium at both sites was fully recovered, showing a normal appearance by LM (Fig 4D). The TEM observations corroborated those of LM.

DISCUSSION

Episodes of upper respiratory tract viral infection often precede or occur concurrently with OM.[1-3] It is a widely held belief that this predisposition is the result of respiratory virus–induced ET epithelial disorders. Previous studies of influenza A virus infection on respiratory epithelium have revealed abnor-

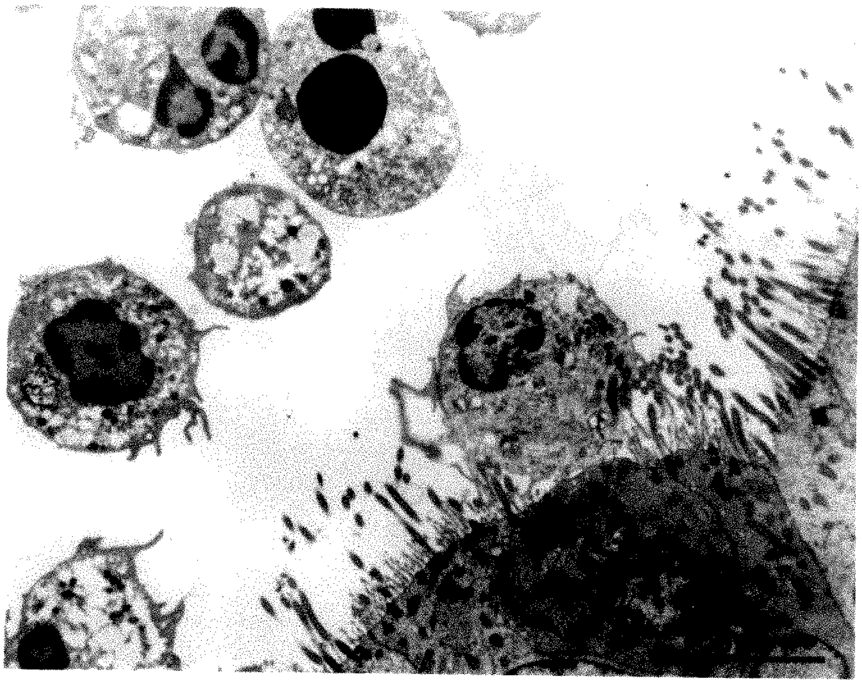

Fig 3. Transmission electron micrograph of eustachian tube epithelium 1 day after transbullar viral inoculation. Note inflammatory cells in tubal lumen.

mal cilia,[4] damage to ET ciliated cells,[8,9] metaplasia of ET epithelium,[9,16] negative middle ear pressure,[7] and dysfunctional peripheral PMNs.[5,6] Giebink et al[20] have demonstrated a significant increase in *Streptococcus pneumoniae*–induced experimental OM in chinchillas inoculated simultaneously with influenza A virus versus those receiving bacteria alone. Data obtained in our laboratory have demonstrated that after transbullar inoculation of influenza A virus, maximal ET pathologic changes with gross infiltration of inflammatory cells occur within 48 hours of inoculation, with recovery beginning at 5 days and continuing to 28 days.[9,16] In this study we have successfully assessed the functional correlates of noted disorders with both a dye transport assay[18] and an in vitro ciliary activity measurement system.[17] It was of additional interest to demonstrate any differences induced by route of inoculation (intranasal versus transbullar), since it is critical, when attempting to answer questions regarding the pathogenesis of human disease with an animal model, to mimic the disease parameters as closely as possible.

In this study we have found that the route of inoculation did affect the histopathologic findings. As expected, transbullar inoculation resulted in more dramatic and immediate damage in the tympanic portion of the ET than at the pharyngeal site. Conversely, intranasal inoculation induced a slightly delayed disorder with equal intensity at both the pharyngeal and tympanic sites of the ET. Regardless of the route of viral inoculation, however, the histopathologic lesions, with the presence of cellular debris in the ET lumen, focal loss of ciliated cells, and the presence of abnormal cilia, were similar, and all increased over time and were then eventually resolved. An additional notable difference between the 2 routes of inoculation, however, was the much more extensive subepithelial inflammatory infiltrate noted in tissue sections obtained from transbullarly inoculated animals, which correlated well with the observation of large numbers of PMNs in bulla lavage fluids recovered from this cohort of animals. Observations made by electron microscopy confirmed these LM observations, as well as those previously reported from this laboratory.[9,16]

Assessment of functional aspects of the ET epithelium correlated well with histopathologic data indicating a more rapid progression of the epithelial disorders following transbullar inoculation than of those observed after intranasal inoculation. While the transbullar route resulted in a more dramatic effect at the tympanic site, the intranasal route affected each site similarly. This difference in the disorders could be due to variable distribution of the viral inoculum as it was instilled, or to the difference in relative densities of ciliated cells at each site, which could affect attachment of this ciliotropic virus.

Dye transport assessment performed on transbullarly inoculated animals yielded findings consistent with both microscopic observations and assessment of ciliary activity. In all experiments, normal status was achieved by 28 days postinoculation, with the exception of the CBF recorded for the tympanic portion of the ETs of intranasally inoculated animals, which was still significantly below baseline values. Despite significant diminution of CBF and dye trans-

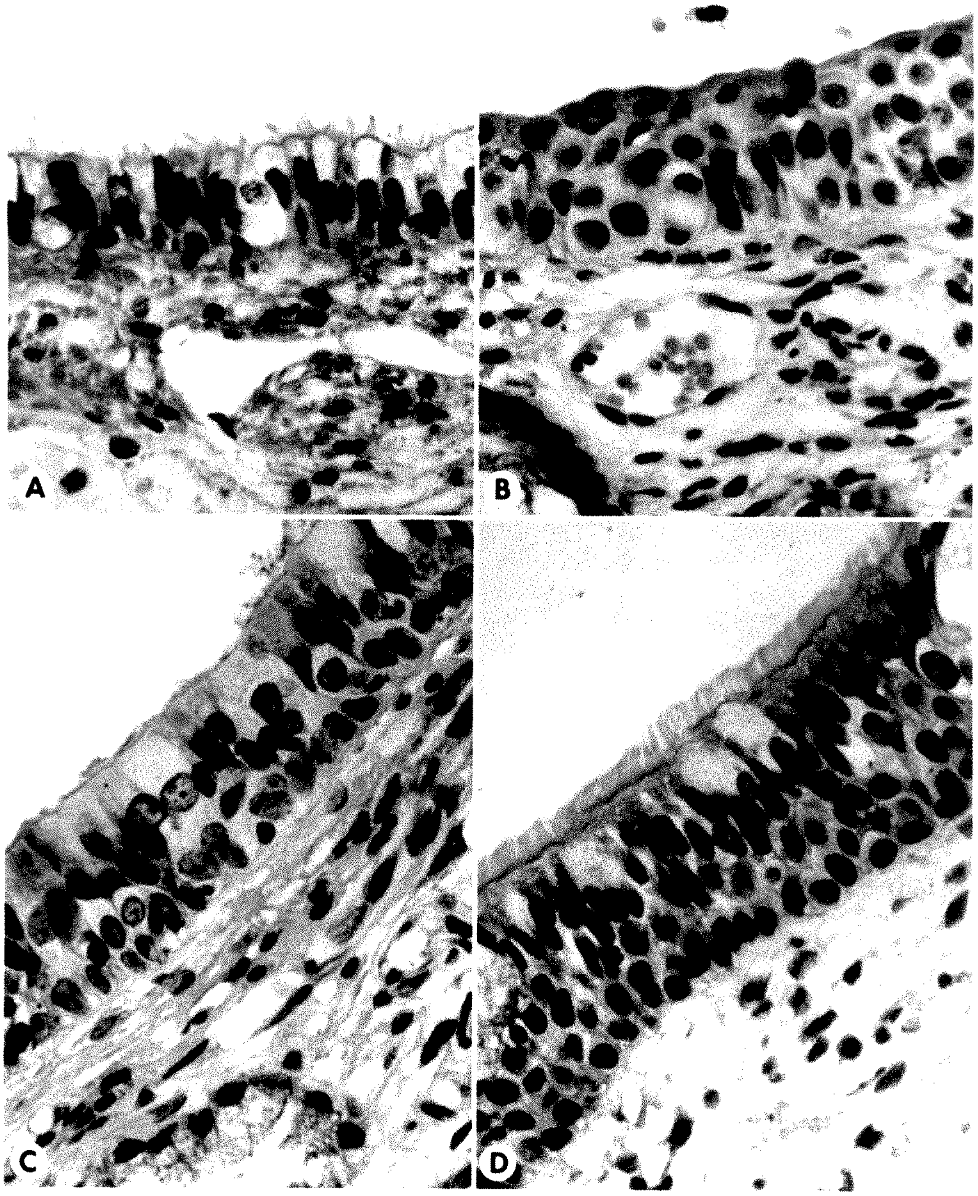

Fig 4. Light micrographs of chinchilla eustachian tube epithelium after intranasal inoculation of influenza A virus (original x64). A) Two days postinoculation, tympanic site. B) At 4 days, pharyngeal site. Note focal loss of ciliated cells. C) At 10 days, pharyngeal site. Note short, regenerating cilia. D) At 28 days, pharyngeal site. Note normal appearance of epithelium.

port values for both cohorts of animals, the presence of MEFs was not a hallmark finding in either this study or our previous studies.[9,16] Giebink et al[8,20] similarly noted only rare middle ear effusions in chinchillas after intranasal inoculation of influenza A virus. Clearly, the development and subsequent retention of fluid in the tympanum is a multifactorial process, and while viral-induced reduction of ET function to below baseline values would likely inhibit clearance of MEFs, if present, this phenomenon did not result in the production of such fluids in this study. It is important to note, however, that the chinchilla, with a semipatulous ET,[21] while useful in many ways as a model of human middle ear disease, may not, however, be an appropriate model for assessment of viral induction of MEFs.

Despite overall low recovery rates of virus in this study, several observations supported the concept that the induced changes were virus-specific. Most notable was the fact that both routes of inoculation of influenza A virus resulted in marked histopathologic and functional changes in the chinchilla ET for up to 21 days postinoculation that were not seen in controls. When culturable, lavage fluids were virus-positive for up to 7 days postinoculation, in keeping with previous studies from this[9,16] and other laboratories.[8,20] Our inability to culture virus from any site 24 hours after inoculation could be coincident with the viral eclipse phase, whereas that occurring after day 7 is most likely attributed to viral clearance in this model. It is interesting to note that NP lavage fluids were much more likely to yield virus-positive cultures than bulla lavage fluids regardless of route of inoculation; this finding may reflect the virus's ciliotropic nature and the increased availability of this cell type at this site compared to that in the middle ear.

In conclusion, we have demonstrated that histopathologic changes induced by inoculation of influenza A virus are mirrored by diminished ET mucociliary activity and transport function. While the natures of the histopathologic lesions were indistinguishable, the different routes of inoculation used in this study did influence various parameters of the resultant disease, and these should be considered when attempting to use the chinchilla as a model of the pathogenesis of influenza A virus as it relates to the development of OM. This virus-induced mucociliary system impairment of the tubotympanum could be a basis for the pathogenesis of bacterial OM and would have an impact on the course of both acute and chronic OM.

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BACTERIAL FLORA IN THE EXTERNAL EAR CANAL AND IN INDUCED CHOLESTEATOMA IN THE MONGOLIAN GERBIL

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We report on the bacterial flora of the external ear canal and of induced aural cholesteatoma in 14 Mongolian gerbils *(Meriones unguiculatus).* In the control, nonmanipulated external ear canal, gram-positive and gram-negative organisms were isolated. In the contents of the cholesteatoma sac, only monomicrobial, gram-negative isolates were found; in each animal they were different from the isolates from the nonmanipulated external ear canal. Obligate anaerobes were absent in all cases. Ligation of the external ear canal in the left ear provoked cholesteatoma in all cases.

KEY WORDS — bacterial flora, cholesteatoma, external ear canal.

INTRODUCTION

Numerous experimental animal studies have been performed on cholesteatoma. McGinn et al[1] reported on aural cholesteatomas caused by ligation of the external ear canal (EEC) in 1982 in the Mongolian gerbil, *Meriones unguiculatus*. The gerbil is a small rodent that lives in the arid steppes of northern China and Mongolia,[2] with an adult body weight of 70 to 100 g.[3] It has a large auditory bulla that occupies around 45% of the cranial base[4] as a distinctive feature. Some investigators think that this facilitates the mechanical transformation of sound and increases auditory sensitivity (for predator evasion), especially for the lower frequencies, by decreasing middle ear impedance.[2] This animal is easy to handle, and its large bulla has a thin bone that facilitates penetration into the middle ear cavity[5] for studies of otitis media,[6] the pathogenesis of cholesteatoma, osteolysis, and the inner ear.

The purpose of the current study was to reveal the bacterial flora in induced aural cholesteatoma in the gerbil and compare it to that in the nonmanipulated contralateral EEC.

MATERIAL AND METHODS

Bacteria were recovered from the nonmanipulated right EEC and from the contents of the induced aural cholesteatoma sac in the left ear in 14 Mongolian gerbils from Estudi General de Lleida Facultat de Medicina. Their ages ranged from 18 to 24 months, and their body weights were 62 to 90 g, with an average weight of 76 g. Each rodent was anesthetized with thiopental sodium, 70 mg/kg body weight, intraperitoneally. The right ear was inspected and used as a control ear. The left EEC had been ligated with a 4-0 silk suture through a C-shaped incision behind the pinna, between 14 and 20 months before. Careful dissection was done to avoid any injury to the facial nerve. All procedures was done with a Zeiss OpMi-1 microscope and with basic microsurgery instruments.

After making a T-shaped incision over the cranium, we elevated the scalp inferiorly and cut the membranous EECs of both ears with Westcott scissors. Then we obtained bacteriologic samples with a small sterile loop (Trans-Swab) from the right EEC (control) and with aspiration of the contents of the cholesteatoma sac. The samples were placed immediately in an anaerobic carrier (Port-A-Cul, BBL Microbiology Systems). Specimens for aerobic cultures were inoculated into blood agar, chocolate, and MacConkey plates and thioglycolate broth. Bacteria were identified by automatic methods (Sceptor System, Johnston Laboratories, Towson, Md) after 40 hours of incubation. Specimens for anaerobic cultures were inoculated into blood agar and blood agar with hemin–vitamin K–kanamycin and vancomycin plates in an anaerobic medium and inspected daily for up to 5 days.

RESULTS

In the control EECs we found no spontaneous cholesteatoma. The tympanic membrane remained intact in all cases. All ligated EECs developed cholesteatomas, in stages III and IV as described by Orisek

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CULTURE RESULTS

	No. of Isolates
Nonmanipulated external ear canal	
Staphylococcus epidermidis	5
Staphylococcus aureus	3
Klebsiella oxytoca	4
Pseudomonas sp	3
Klebsiella ozaenae	1
Providencia stuartii	1
Enterobacter aerogenes	1
Escherichia coli	1
Serratia liquefaciens	1
Contents of cholesteatoma sac	
Escherichia coli	4
Proteus sp	3
Proteus mirabilis	1
Citrobacter	1
Pseudomonas sp	1
Enterobacter aerogenes	1
Serratia liquefaciens	1
Enterobacter cloacae	1
No growth	1

and Chole.[7] The pars flaccida developed perforations filled with keratin debris that occupied the anterior mastoid chamber and eroded the malleus, the incus, and the ampulla of the superior semicircular canal, to different degrees. The stapedial artery was compressed by cholesteatoma and it became in some cases a fine fibrous tract. We saw marked bone erosion in the bony EEC in the left ear. In 2 induced cholesteatomas a purulent exudate was found. In 4 cases we found a mucoid effusion filling the middle ear cavity.

The results of the cultures (see Table) in the control ear show mainly monomicrobial isolates, gram-positive in 8 specimens and gram-negative in 12 specimens, with no obligate anaerobes. There were no sterile samples among the control ears. In 3 samples gram-negative associations were found.

From within the contents of the cholesteatoma sac, only gram-negative germs were isolated. There was no growth in 1 sample (see Table). Neither polymicrobial flora nor anaerobes were found in the left ear.

DISCUSSION

The EEC control cultures showed colonization by gram-positive and gram-negative organisms without signs of inflammation in all cases. In 3 cases there was an association between gram-negative organisms: 1) *Klebsiella oxytoca, Escherichia coli,* and *Pseudomonas* sp, 2) *K oxytoca* and *Pseudomonas* sp, and 3) *K oxytoca, Serratia liquefaciens, Enterobacter aerogenes,* and *Pseudomonas* sp. In the control ears, 60% of the isolates were gram-negative. Thompson et al[8] found that gram-negative germs were absent for the most part from the cerumen of the EEC. The presence of such a high proportion of gram-negative germs in the EEC of the control ear could probably be due to the contamination of EEC skin by the animal's feces. From what we can see, the colonization of EEC skin is variable, and possibly due to the animal's habitat and the litter, which was changed weekly in our experiment.

We have seen no consistency between the germs isolated from the control EEC and those isolated from the contents of the cholesteatoma sac. Despite our having located a high proportion of *Staphylococcus* in the control ear, it was not present in the cholesteatoma contents. This result was unexpected, as Fulghum and Chole[9] cite *Staphylococcus* as the most frequently located germ in spontaneously occurring cholesteatoma. In our cases only gram-negative organisms were found in the cholesteatomas. The results of Fulghum and Chole, from spontaneous cholesteatomas in the Mongolian gerbil, are mostly polymicrobial, with an average of 3.6 different species, whereas in our study all the samples were monomicrobial. No anaerobes were detected in the cholesteatomas, although these are seen in human cholesteatomas.[10]

In human cholesteatoma and chronic otitis media[10-12] the existence of a high proportion of anaerobic germs is described; one could postulate that self-infection could be related to osteolysis in these cases.[11,13]

In conclusion, the bacteriology of our control EECs was variable, mainly monomicrobial, with gram-positive and gram-negative organisms. We found no correlation between the isolates from the control ear and those from the experimental aural cholesteatoma. No anaerobes were isolated from the control ears or the cholesteatomas.

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FIRST CONGRESS OF EUROPEAN SKULL BASE SOCIETY

The European Skull Base Society will hold its first congress September 26-30, 1993, in Riva del Garda (Trento), Italy. For further information contact Carmelo Zappone, MD, Congress Secretary, Division of ORL, Ospedali Riuniti, Largo Barozzi 1, 24100 Bergamo, Italy; telephone 35-269578; fax 35-269460.

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FOURTH INTERNATIONAL SYMPOSIUM AND WORKSHOPS ON INNER EAR MEDICINE AND SURGERY

The Fourth International Symposium and Workshops on Inner Ear Medicine and Surgery will be held July 17-24, 1994, in Snowmass-Aspen, Colorado. For more information, please contact I. Kaufman Arenberg, MD, Executive Director and Program Chairman, 300 E Hampden Ave, Suite 401, Englewood, CO 80110; phone (303) 788-4320 or (303) 850-9545; fax (303) 788-4234.

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IMAGING CASE STUDY OF THE MONTH

CAROTID SPACE MASS DISTORTING THE PARAPHARYNGEAL SPACE

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INTRODUCTION

Knowledge of the parapharyngeal space (PPS) is paramount in understanding disorders of the suprahyoid neck. The PPS may be thought of as a fatty shaft that extends from the skull base superiorly to the hyoid bone inferiorly with direct communication into the submandibular space.[1] This anatomic arrangement allows tumors or infections from adjacent spaces to spread upward to the skull base or inferiorly into the submandibular space.[1] Because primary lesions of the PPS are rare, the majority of cases thought to be primary to the PPS can be shown to arise from one of the neighboring deep facial spaces.[1] The critical step in localizing a mass of the suprahyoid neck to the pharyngeal mucosal space, masticator space, parotid space, or carotid space is to establish the epicenter of the lesion relative to the PPS and then evaluate the displacement of the PPS fat.[2]

CASE REPORT

A 70-year-old man presented with a 3- to 4-week history of dysphagia and mild voice alterations. Physical examination demonstrated bulging mucosae involving the left nasopharynx. There was no ulceration or pulsation. The neck examination revealed a fullness near the tail of the left parotid gland. A computed tomographic scan of the head performed at another institution was initially interpreted as demonstrating a PPS mass (Fig 1). On review of this study it was noted that the epicenter of the mass was posterior to the PPS. There was a loss of planes between the PPS and the prevertebral muscles. Therefore, the lesion was felt to be more consistent with a carotid space mass. A magnetic resonance examination with gadolinium–diethylenetriamine pentaacetic acid was obtained. T1-weighted images demonstrated the left carotid artery encased by a 6 x 6 x 5-cm mass centered in the left carotid space (Fig 2). Figure 2 shows that the pharyngeal mucosal space is compressed, but there is no evidence of invasion. The parotid and masticator spaces appear to be uninvolved (Fig 2). A fine-needle aspiration was positive for lymphoma.

DISCUSSION

Mass effect on the PPS plays a central role in determining the origin of suprahyoid neck masses. Knowledge of the space of origin is then useful in deriving a differential diagnosis.[1-3] Because of the limited contents of the PPS (fat, branches of cranial nerve V3, internal maxillary artery, ascending pharyngeal artery, and pharyngeal venous plexus), pri-

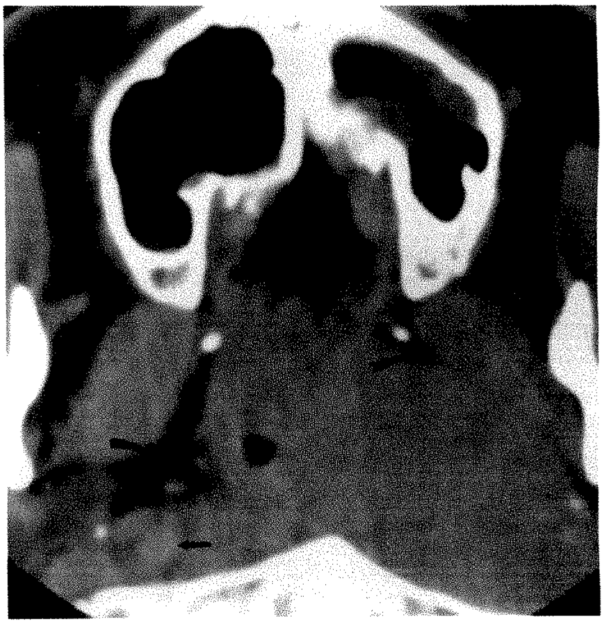

Fig 1. Computed tomogram in axial plane showing normal parapharyngeal space (curved arrow) and carotid artery on right (short arrow). Soft tissue density on left is inseparable from carotid space, pharyngeal mucosal space, and prevertebral muscles. Thin fat plane is lateral to mass (long arrow).

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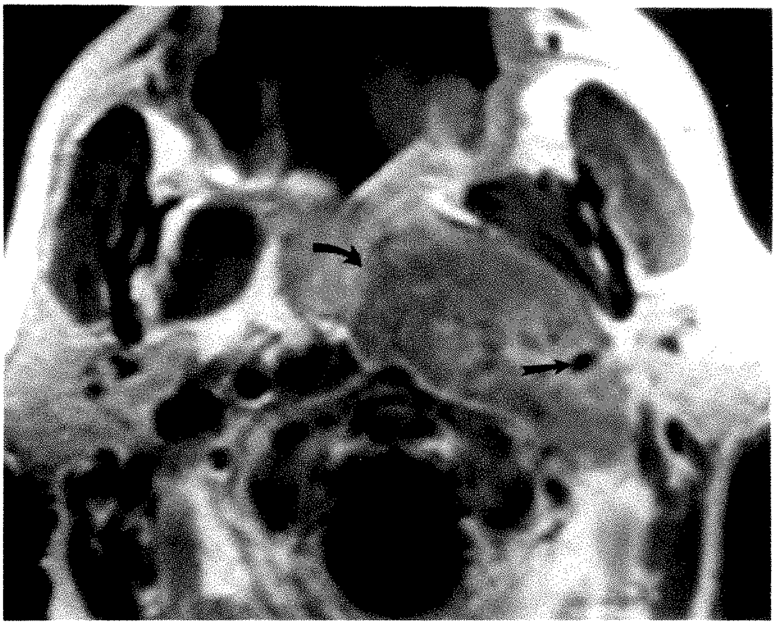
Fig 2. Axial gadolinium–diethylenetriamine pentaacetic acid–enhanced magnetic resonance image demonstrating encasement of left carotid artery by mass (straight arrow). Nasopharyngeal mucosa is compressed but appears intact (curved arrow).



mary lesions of the PPS are rare.[2] Pleomorphic adenoma of minor salivary glands, lipoma, and atypical branchial cleft cysts are the principal intrinsic lesions encountered in the PPS.[1] For a mass to be localized to the PPS, it should be centered within the PPS, and fat planes should separate it from adjacent spaces.[1] The importance of evaluating masses in this area for continuity with the deep lobe of the parotid gland has been emphasized.[1]

A deep lobe parotid tumor primarily involves the lateral aspect of the PPS, at times producing a "crescentic" deformity of the PPS when viewed in the coronal plane.[4] Nasopharyngeal carcinomas primarily involve the medial PPS.[1,4] Carotid space lesions impinge on the posterior aspect of the PPS and may produce an anteriorly convex, "capping" deformity of the PPS in the axial plane.[4] Our case demonstrates the usefulness of analyzing the PPS fat displacement in the evaluation of suprahyoid neck masses. By localizing the epicenter posterior to the PPS, we were able to place the origin of the mass within the carotid space and allow the formulation of an appropriate differential diagnosis.

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IMAGING CASE STUDY OF THE MONTH

TRAUMATIC CERVICAL CYSTIC LYMPHANGIOMA IN AN ADULT

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INTRODUCTION

Cystic lymphangiomas (hygromas) are uncommon lesions for which the magnetic resonance imaging (MRI) characteristics have been described recently.[1,2] These lesions are thought to represent congenital abnormalities of the lymphatic system that usually present in children before the age of 2 years. However, there have been reports of cystic lymphangiomas presenting in adults as a sudden-onset, enlarging mass.[3-8] Although trauma has been suggested as a possible cause for the development of cystic lymphangiomas in adults, a review of the literature revealed only 1 case in which trauma was thought to be the cause.[3]

We present a case in which a 66-year-old man developed a neck lesion as a result of trauma. The lesion initially was diagnosed as a traumatic cystic lymphangioma on the basis of clinical history and characteristic MRI appearance, and this diagnosis was proven by incisional biopsy. To our knowledge, this is the first report describing the MRI findings of a traumatic cystic lymphangioma.

CASE REPORT

A 66-year-old man noticed progressive swelling along the right side of his neck after a work-related accident in which he fell approximately 6 m onto a concrete floor, breaking several ribs. There was no history of a mass or injury in this region before the accident. Initially, it was thought to be a hematoma and was aspirated, with pathologic findings consistent with the diagnosis. However, the mass gradually increased in size over the next 4 months and the patient finally sought treatment from an otolaryngologist. The examination revealed a mobile mass, measuring approximately 9 cm, extending from the neck into the right supraclavicular region, that was firm, nonerythematous, and nontender. A hematoma was suspected and a neck computed tomography (CT) scan was obtained without contrast material because of renal insufficiency, The CT scan demonstrated a large mass in the right anterior triangle, lateral to the carotid sheath, extending from the level of the mandible into the supraclavicular space. The lesion was somewhat heterogeneous; however, most of the lesion was near fluid attenuation. An MRI scan of the cervical region revealed a large, multiloculated right neck mass located lateral to the carotid sheath and displacing the carotid artery slightly medially. The mass was situated just below the level of the body of the mandible and extended into the right supraclavicular space without any evidence of mediastinal extension (Fig 1). The signal characteristics of the mass were heterogeneous, but showed predominantly hyperintensity on both T1- and T2-weighted images.

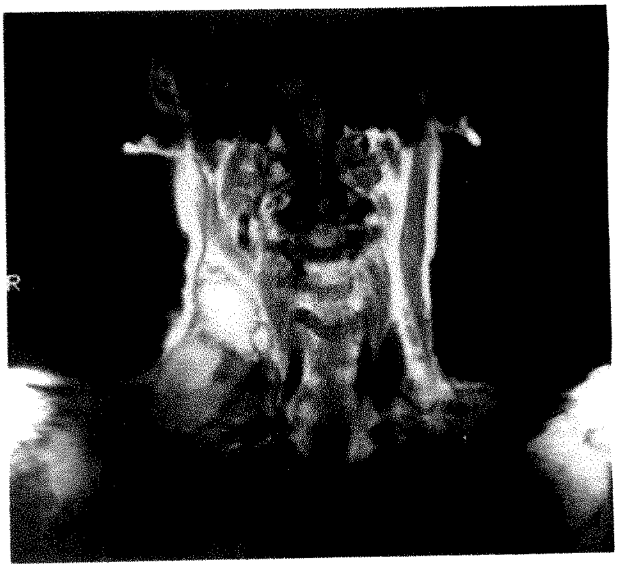

Fig 1. Coronal T1-weighted image showing caudal extension of lesion into supraclavicular space without mediastinal involvement. Areas of extreme hyperintensity may represent focal blood collections demonstrated at incisional biopsy.

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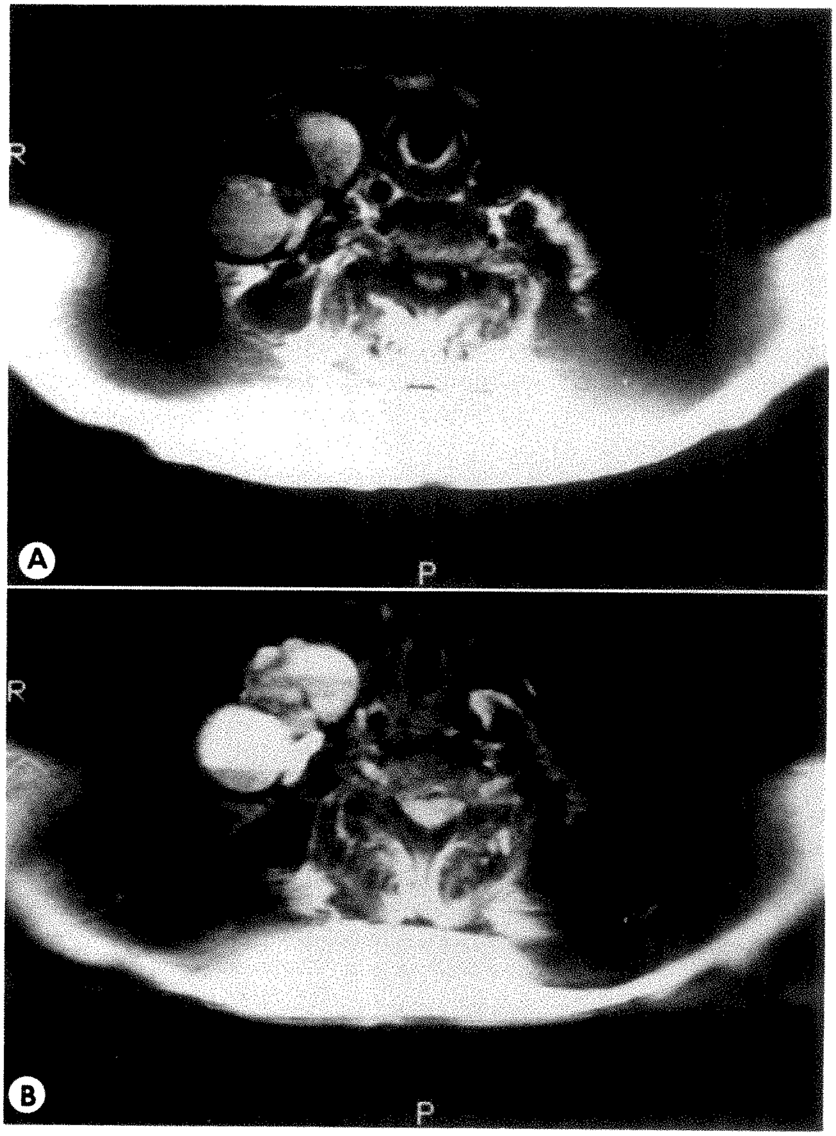

Fig 2. Axial A) T1-weighted (TR/TE/NEX = 600/20/1) and B) T2-weighted (2,000/100/1) images showing large, heterogeneous, multicystic neck mass with multiple fluid-fluid levels. Signal of fluid in nondependent layers has much higher intensity than that in dependent layers.

Multiple fluid-fluid levels with variable higher signal intensity in the nondependent layers consistent with signal exhibited by the blood by-products were also demonstrated (Fig 2). On the basis of this characteristic MRI appearance and the clinical data, the diagnosis of probable cystic lymphangioma was made. This lesion was removed at surgery, and pathologic confirmation of cystic lymphangioma was made.

DISCUSSION

Lymphangiomas are relatively rare congenital abnormalities of the lymphatic system. These lesions usually present in infants and children; 65% manifest at birth and 90% are clinically apparent before 2 years of age.[9] However, lymphangiomas have been reported to present in all decades of life.[3-8] The neck is the most common location for these lesions, accounting for about 75%; 20% occur in the axilla; and the remainder are found in the retroperitoneum, mediastinum, groin, pelvis, and abdominal wall and within muscle.[1,7-9] Most lymphangiomas in children involve the neck, presenting as asymptomatic masses that usually cause only cosmetic problems. Occasionally, these lesions can cause respiration and swallowing difficulties. In contrast, the lymphangiomas that occur in deeper locations such as the mediastinum and retroperitoneum usually present in adults, often as an incidental finding.[3,5,7,8] They usually go undetected because they are asymptomatic. Lymphangiomas can be classified into 3 main histologic types: 1) simple, composed of many small lymphatic channels; 2) cavernous, composed of dilated lymphatic channels; and 3) cystic hygroma, composed of cystic spaces containing lymphatic fluid.[10,11] However, it is not uncommon for elements of all 3 types to be found in the same lesion.[12]

The exact cause of lymphangiomas is still disputed. Attempts have been made to explain the development of these lesions on the basis of the embryology of the lymphatic system. Dowd,[13] among others, has proposed that lymphangiomas develop as a congenital sequestration of lymphatic tissue from one of the primitive sacs that fails to develop its normal drainage channels. It is believed that these sequestrations of primitive lymphatic tissue retain their embryonic potential for rapid and irregular growth. This would explain why most lymphangiomas are found near the primitive sacs, with the neck being the most common location and the region in which the lymphatic system is most extensive and complex. The explanation for the onset of an enlarging cervical lymphangioma in adults is less clear. Some investigators[4] propose that these lesions represent the spontaneous enlargement of previously existing but subclinical lesions.[4] Others implicate specific inciting factors such as infection, tumor, or trauma.[3] There has been only 1 reported case of cystic lymphangioma associated with trauma in the literature, and our case is the first with MRI findings.

The MRI appearance of childhood lymphangiomas has been described recently.[1,2] Cystic lymphangiomas are usually multilocular with visible septations, and fluid-fluid levels within cysts have higher-intensity fluid in the nondependent layers.[2] They appear heterogeneous on both T1- and T2-weighted images. Depending on the contents and degree of the cystic component, they can show an intensity that ranges from greater to slightly less than that of muscle on T1-weighted images, and is greater than that of muscle on T2-weighted images. Although our case was associated with trauma, the fact that the MRI appearance is similar to that described for typical cystic lymphangiomas suggests that the growth and behavior are almost the same.

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PATHOLOGY CONSULTATION

EPITHELIAL CHORISTOMAS AND TERATOMAS OF THE TONGUE

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Nonsalivary choristomas of the oral cavity are rare, have a predilection for the tongue, and are classified according to their generative tissues as gastroenteric, thyroidal, or sebaceous. Only the lingual thyroid choristoma has a malignant counterpart. Lingual teratomas are even rarer. They have been histologically benign.

A choristoma is a tumorlike mass of normal cells in an abnormal location.[1] It differs from a hamartoma, which is a focal overgrowth of normal cells that are indigenous to the site of involvement.[1] Each, in turn, is different from a teratoma. Teratomas are tumors composed of tissues, often alien to the site of involvement, arranged in a haphazard or confused manner. There is also anomalous differentiation of the constituent tissues, but abortive attempts at organogenesis may be noted.[1]

A variety of choristomas and teratomas occur in and about the oral cavity, and the choristomas have been classified by Chou et al[2] (see Table). The nonsalivary epithelial choristomas have a predilection for the tongue, but the tongue per se is an uncommon site for teratomas. The following is a contemporary assessment of lingual epithelial choristomas and teratomas.

GASTROENTERIC CHORISTOMA

Approximately 30 examples of this type of oral choristoma have been reported — 21 of them between 1960 and 1991.[2] The lesions may be cystic or solid, with the majority being cystic. Nearly all have been lingual, preponderantly of the ventral tongue, with extensions to the floor of the mouth. Less often, the choristomas are confined to the floor of the mouth.

Usually presenting as asymptomatic swellings or masses (1 to 3 cm in diameter), the choristomas are generally diagnosed in infancy or early childhood, but may be unrecognized until early adulthood.[2]

The cystic lesions are most often lined by an epithelium that is histologically that of the cardiac, fundic, or pyloric regions of the stomach. Metaplastic (squamous) zones and ciliated columnar cells may be present. Besides the gastric-type epithelium, an intestinal and even colonic mucosa may be imitated. A continuous or interrupted smooth muscle layer is often seen outside the mucosa of the cyst. Solid gastroenteric choristomas have the same cellular constituents as the cystic lesions, but are polypoid and less circumscribed (see Figure).

In the 4-week embryo, the undifferentiated primitive stomach lies in the midneck region close to the tongue primordium.[2] It is believed the gastroenteric choristomas originate from entrapped endodermal precursors of the stomach.[2]

Conservative surgical excision is the treatment; recurrences are unusual.[2]

LINGUAL THYROID CHORISTOMA

This type of choristoma is to be distinguished from a simple ectopia of thyroid tissue. The latter are asymptomatic, microscopic remnants of the thyroid precursor at the base of the tongue and have been found in 10% of routine necropsies.[2] The lingual thyroid choristoma arises from these ectopic foci and

CLASSIFICATION OF CHORISTOMAS OF ORAL REGION

- Salivary gland
  - Central (intraosseous)
  - Gingival
- Supporting tissue
  - Cartilaginous
  - Osseous
- Lingual thyroid
- Lingual sebaceous
- Glial
- Gastroenteric mucosal

Modified from Chou et al.[2]

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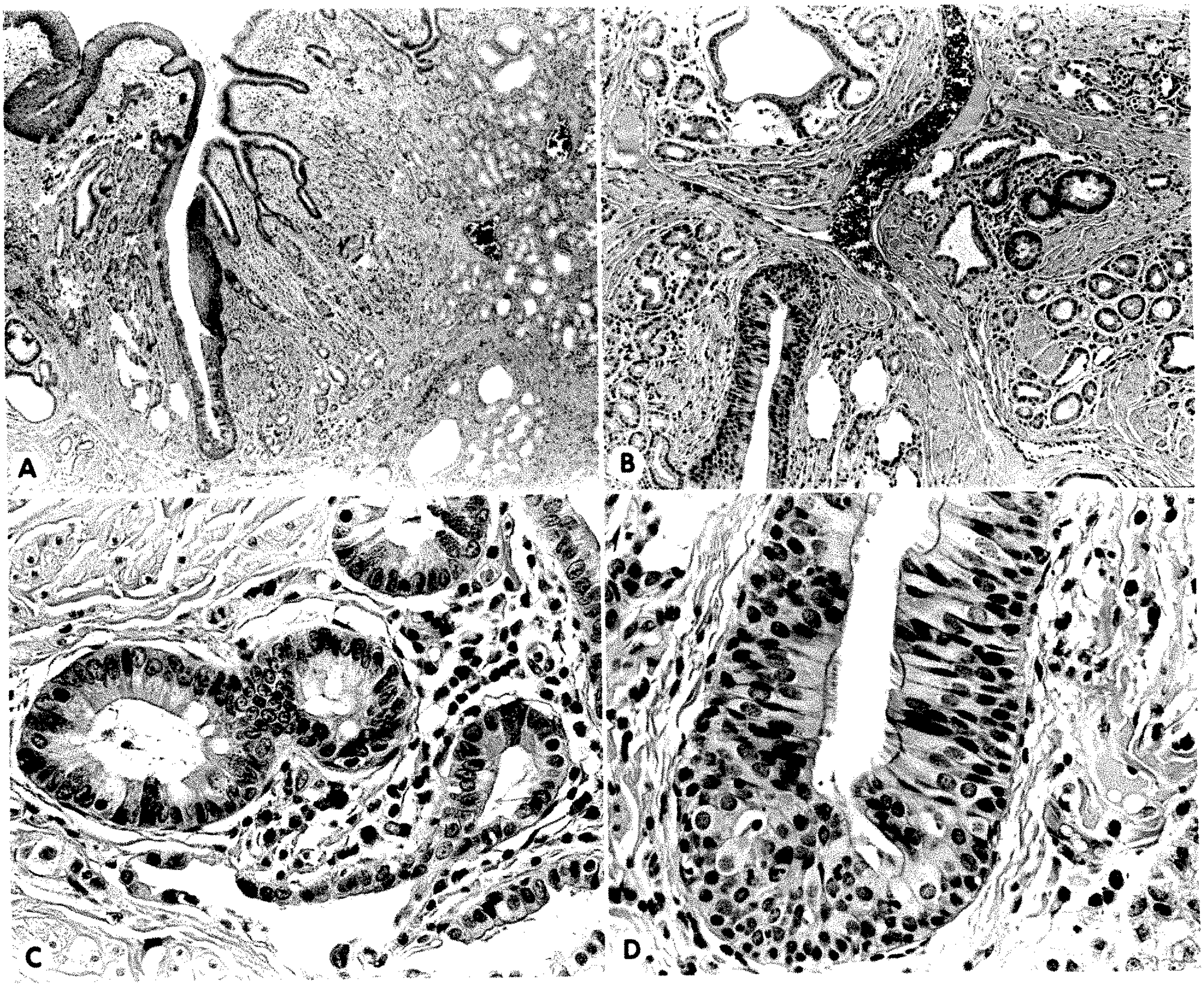

Solid gastroenteric choristoma of anterior (tip of) tongue. A) Polypoid collection of gastric-type glands and smooth muscle (H & E, original x25). B) Smooth muscle bundles separate gastric glands and duct with ciliated cells (H & E, original x50). C) Gastric glands with Paneth's cells (coarse granular cytoplasm; H & E, original x200). D) Ciliated cells in gastroenteric choristoma (H & E, original x200).

forms a tumor. This rare event may be associated with total thyroid gland ectopia. In 42 of the 49 (86%) cases reviewed by Chou et al,[2] the choristomatous lingual thyroid was the only functional thyroid tissue in the patient.

The female-male ratio for lingual thyroid choristomas is 4:1, whereas that for nonchoristomatous ectopias is 9:11.[2]

Thyroid choristomas are in the median line of the tongue's base, between the foramen cecum and the epiglottis.[3] They are globoid, semisoft to firm, lobulated masses covered with an intact mucosa and may be as large as 5 cm when diagnosis is made. The signs and symptoms of lingual thyroid choristomas depend on the size of the lesion and whether it is the only functioning thyroid tissue. The majority of cases are asymptomatic and found on routine oral examination. Others cause signs and symptoms of dysphagia, dysphonia, dyspnea, hoarseness, and a sensation of a lump in the throat. The tumors are nearly always painless.[2,3]

Functional thyroid disorders can be associated with the lingual choristomas. Hypothyroidism is more frequent than hyperthyroidism. According to Chou et al,[2] hyperthyroidism has been noted only when there is also a functioning thyroid gland in its normal pretracheal location.

Imaging procedures usually obviate the need for a biopsy diagnosis. Indeed, biopsy may be contraindicated because of the morbidity. When biopsy tissues have been procured, they can manifest all of the possible retrogressive, cystic, and inflammatory changes seen in the normal thyroid gland. Most often, however, a microfollicular or fetal adenomatous pattern, alone or mixed with mature follicles, is exhibited.[2]

Symptomatic lingual thyroid choristomas are best treated by nonsurgical means, eg, radioactive iodine or thyroid hormone suppression to reduce the size of the lesion.[2]

Carcinoma arising in lingual thyroid tissue is rare.[2,3] It has been estimated to occur in 1% of ectopic lingual thyroids.[4] Between 1910 and 1992 there were only 22 reported cases.[4] The highest incidence is in the third decade of life. Surprisingly, none of the cases have been papillary carcinomas.[4]

SEBACEOUS CHORISTOMA

Approximately 80% of the population is said to manifest so-called ectopic sebaceous glands in the oral cavity, especially on the buccal and labial mucosa, palate, gingiva, and retromolar areas.[2] The tongue, on the other hand, has been the site of sebaceous choristomas, which have ranged in size from 0.2 to 2 cm in diameter in the 6 reported examples.[2] The dorsal posterior tongue and middle third of the tongue have been the sites of involvement.

These asymptomatic choristomas are composed of differentiated sebaceous glands with excretory ducts tending to open on the surface. There may also be other parts of the pilosebaceous apparatus and thyroglossal duct–like structures.[2] The choristomas are histologically and biologically benign.

TERATOMA

Teratomas of the head and neck constitute 2% to 9% of all teratomas.[5] The usual head and neck sites of involvement are the nasopharynx and the cervical region. Oral and especially lingual teratomas are rare. The 7 reported teratomas of the tongue presented at birth and without an area of predilection.[5] The size of the teratomas has varied from 1 x 2 cm to 10 x 12 cm. The malignant potential of teratomas of the tongue cannot be fully assessed because of short follow-up periods. Histologically, the tumors have been benign.[5]

Treatment is complete surgical excision. Recurrences have not been recorded.

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Complications in Head and Neck Surgery

Yosef P. Krespi and Robert H. Ossoff, editors. Hard cover, illustrated, indexed, 582 pages, 1993. WB Saunders, Philadelphia, Pa, $85.

The primary purpose of a book on surgical complications should be to help the physician prevent, recognize, and manage undesired side effects and results. Such a book should preach that prevention of complications begins at the preoperative level with patient selection and evaluation of the need of surgery and extent of the procedure. Furthermore, it should pronounce that professional competence in surgical techniques and postoperative care should be achieved to minimize the incidence of complications. While few of the 54 contributors to this book "preach," each conveys this information, thus fulfilling these purposes.

Although 3 chapters deal with generally related subjects (anesthesia, laser surgery, and acquired immunodeficiency syndrome), each of the 31 chapters is devoted to a specific surgical condition. Following a brief general introduction of the condition, the reader is led directly to the possible preoperative and postoperative complications related to it. The authors have ample opportunity to develop variations on this format. Some essays are overdone, bringing to mind 2 of the precepts of Dr John Shaw Billings, the eminent founder of the National Library of Medicine and Index Medicus, who conveyed this rule to an aspiring scientific author: Say it and stop as soon as you have said it.

The format may well be the most outstanding feature of this book, as it allows sought-after solutions to be easily located. Two authors benefit from deviating from the format, however. Those writing on cleft lip surgery show photographs of undesirable results and concisely pursue the cause and preventive measures, and the author of Rigid Endoscopic Procedures points out the significance of recognizing a complication and then pursues the options for appropriate care.

While the editors have assembled a wide range of current knowledge of their subject, they do not include the particular complications of otologic surgery. Rather, the reader is offered 2 chapters, written by different authors, on skull base surgery.

This book responds to the continuing need for information on surgical complications, and will be an invaluable teaching and review source for clinicians. The last book reviewed for this journal on the topic was published in 1986, so it is time for such a work.

Dennis G. Pappas, MD
Birmingham, Alabama

Tinnitus Diagnosis/Treatment

Abraham Shulman, Jean-Marie Aran, Juergen Tonndorf, Harald Feldmann, and Jack A. Vernon. Hard cover, illustrated, indexed, 571 pages, 1991. Lea & Febiger, Philadelphia, Pa.

The main attribute of this book is that it is a worthy reference chronicle. The cause, mechanism(s) of action, most definitive diagnostic procedures, and most efficacious treatments of tinnitus are well reviewed and generously augmented by bibliographies.

The 4 sections of the text are presented in a logical order: historical review, review of the basic science of the auditory system, diagnosis, and treatment. The text is made homogeneous by the authors' apparent agreement on the cause and mechanism of action of tinnitus: dyssynchronous neural firing between outer and inner hair cells (at the same level) caused by an insult. Dr Juergen Tonndorf presents a good review of this theory in his chapter The Origin of Tinnitus.

Included in the wide variety of aspects of tinnitus covered in this text is objective tinnitus, which is treatable. Polycythemia vera, hyperviscosity syndrome, sickle cell disease, otosclerosis, sudden hearing loss, temporomandibular joint syndrome, presbycusis, renal disease, and other conditions that may be accompanied by tinnitus are also covered. In what appears to be divergent from the format of this book and its comprehensive coverage, however, benign intracranial hypertension is not mentioned in the chapter on the clinical types of tinnitus. Instead, it is presented in the section on specific causes as a neurologic diagnosis. Since this condition has received increased attention in recent literature, it would seem to deserve better organization and elucidation.

The senior author (Dr Shulman), with and without colleagues, writes extensively on the use of auditory brain stem response (ABR) evaluation techniques in tinnitus patients. The text suggests that ABR for the patient with subjective idiopathic tinnitus (SIT) is of both diagnostic and remedial value. The author concludes that by ruling out the ABR diagnostic criteria for central tinnitus, a default diagnosis of peripheral tinnitus can be made. By traditional (largely subjective) techniques, only 25% of tinnitus patients fitted with various types of instrumentation will improve. The premise that ABR may aid in identifying clinical types of tinnitus, maskability, selection of ear of choice for fitting maskers, and effectiveness of instrumentation used is interesting and provocative. While the ABR diagnostic protocol presented for SIT patients provides an excellent basis for further research, it would appear that the value of this approach awaits more controlled studies. Factors such as age and degree of hearing loss received insufficient attention as the definitive cause for dyssynchronous ABR waveform morphology. In order to overcome the effect of dyssynchrony of the waveform, the ABR technique described involves increasing the number of recordings as well as of sweeps. Given the large numbers of patients presenting with SIT — a substantial number of whom may have inherent dyssynchrony of ABR waveforms due to advanced age, high-frequency hearing loss, etc — clinical application of the ABR evaluation technique may have limited practicality without further research and cross-validation.

This book also presents the use and effect of different drug therapies on tinnitus, including phenytoin sodium (Dilantin), propranolol (Inderal), antihistamines, and intravenous lidocaine. Descriptions of the anatomy and physiology of the auditory system, while covering a great number of generalities, provide a good source of references.

The conscientious efforts displayed by these authors in their coverage of the complex topic of tinnitus should be appreciated. For the general otolaryngologist and clinical audiologist, most of whom are in search of concise, pragmatic information, the descriptions of disease processes such as autoimmune inner ear disease may be too involved. However, such information may be of value to those in other fields of medicine and may stimulate further research by our colleagues.

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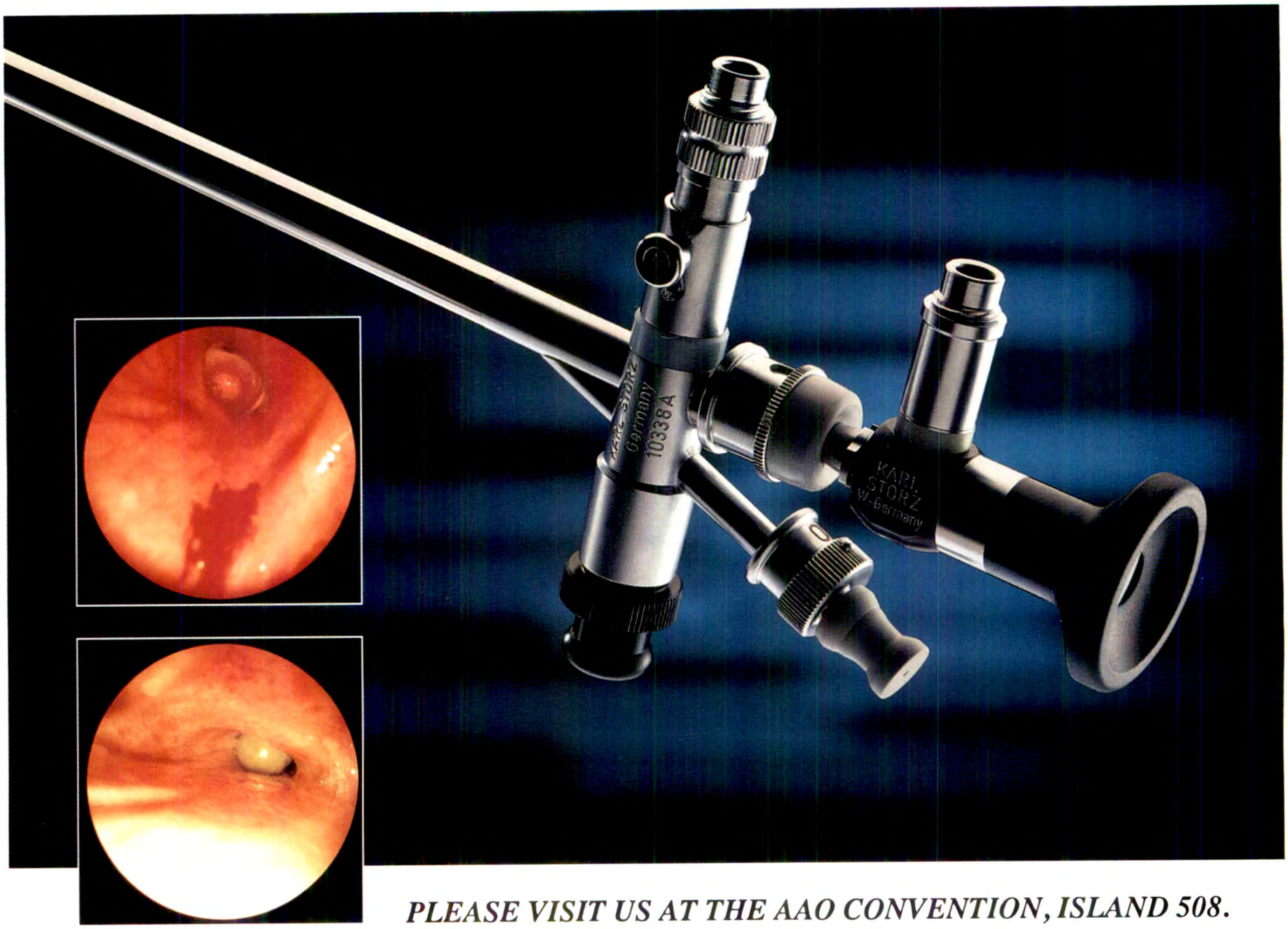

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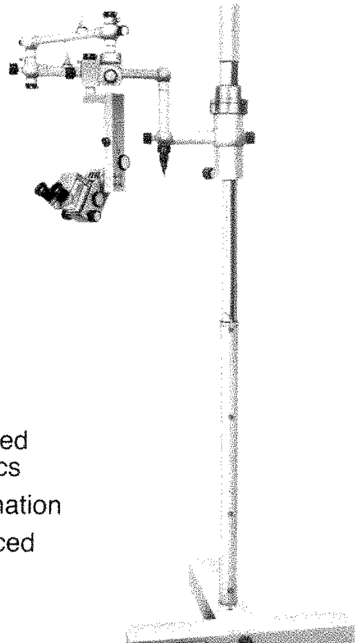

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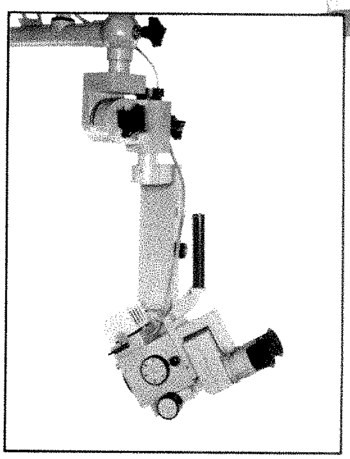

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WHOLE ORGAN EVALUATION OF COLLAGEN IN THE DEVELOPING HUMAN LARYNX AND ADJOINING ANATOMIC STRUCTURES (HYOID AND TRACHEA)

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The collagen composition (types I, II, and III) of the normal developing human larynx and trachea was examined by biochemical methods. Autopsy specimens of larynges with attached upper tracheal rings were obtained from 28 humans ranging in age from birth to 44 years. The specimens were randomly collected, but excluded if laryngeal disease existed. The age, sex, and cause of death were documented. Collagen is important in the growth, development, repair, regeneration, and structural and functional integrity of the laryngeal framework. A preliminary report of selected cartilaginous components of the larynx was previously published by the authors, which studied the changes in the phenotypic expression of the collagen genes in children from the newborn period to 5 years 10 months of age. The current study included all of the functioning components of the skeletal larynx and trachea. The results of biochemical examination of these tissues are reported, and the potential clinical significance of the results of the study is discussed.

KEY WORDS — collagen, connective tissue, human larynx, laryngeal growth and development.

INTRODUCTION

It was with the appearance of a cartilage plate in the evolutionary development of the human larynx that collagen was heralded as an important factor in establishing the architecture, strength, and functional integrity of this conduit and protector of the lower airway. Further development of more specialized cartilages gave importance to the development of other functions of the larynx.

Studies of the comparative anatomy of the larynx indicate that cartilage first appeared in the African mudfish (*Protopterus*), as a flat plate for the purpose of stabilizing and strengthening muscle constriction. With the addition of newer cartilages, the complexity of these cartilaginous structures gave rise to the larynx as seen in humans, and permits advanced functions.[1]

The purpose of this study is to quantify the phenotypic expression of the genetically distinctive types of collagen: I, II, and III. The study evaluates the collagen distribution of the entire intrinsic human larynx; the hyoid, when specimens were available; and the trachea during its development from birth to adult life. With these results, it will be possible to compare disorders of collagen in connective tissues with these established norms.

BIOCHEMISTRY OF COLLAGEN

The biochemistry of normal collagen has been detailed in a previous paper by the authors.[2] In summary, the chief function of protein is its structural role.[3,4] While each collagen has a specific purpose, this is as yet not completely understood. An understanding of the normal type I, II, and III collagens and their content within the normal laryngeal structure is essential, so as to be able to understand diseases in which inadequate or excessive accumulations of collagen occur and/or in which there are changes in collagen type.

The three interstitial collagens, types I, II, and III, are the main types found in connective tissues. Type I collagen is the most prevalent type found in the vertebrate organism. Type II collagen is the predominant collagen found in hyaline cartilage. Type III collagen is found in association with the larger type I fibers in the more distensible connective tissues such as skin and arteries.

MATERIALS AND METHODS

Of the 28 specimens collected, 18 were male and 10 were female. The age at death varied from 11 hours to 44 years (1 specimen). Of the total number, 8 were from neonates (under 30 days of age), 6 were

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from infants 1 to 12 months of age, 7 were from children 1 to 6 years of age, 6 were from children 7 to 12 years of age, and 1 was from an adult 44 years of age. The causes of death were as follows. Eight deaths were due to sepsis, 5 to meningitis, 3 to bronchopulmonary dysplasia, and 2 to malignant tumors. One death was due to each of the following: congenital heart disease, acquired immunodeficiency syndrome, pulmonary tuberculosis, immunodeficiency, bronchopneumonia, leptospirosis, meningitis, disseminated intravascular clotting, bacterial meningitis, intestinal dysplasia, and prematurity.

Whole organ autopsy specimens of the larynx were randomly collected and included the upper tracheal rings and, when available, also the central portion of the body of the hyoid bone. To prevent drying, the specimens were wrapped and immediately frozen and stored at –70°C. The age and sex of the patient were documented. Excluded from the study were larynges with associated intrinsic laryngeal disease.

After defrosting, the specimens were immediately dissected so as to remove all attached extrinsic musculature and ligaments and to outline the laryngeal and tracheal cartilaginous skeleton. Each component of the skeletonized larynx was then sampled for biopsy, and samples were placed into a vial containing chloroform-methanol (50/50, vol/vol). The specimens were labeled for identification and immediately refrigerated at temperatures of 2°C to 6°C awaiting transfer to the laboratory.

Each larynx was then dissected and specimens were obtained as follows:

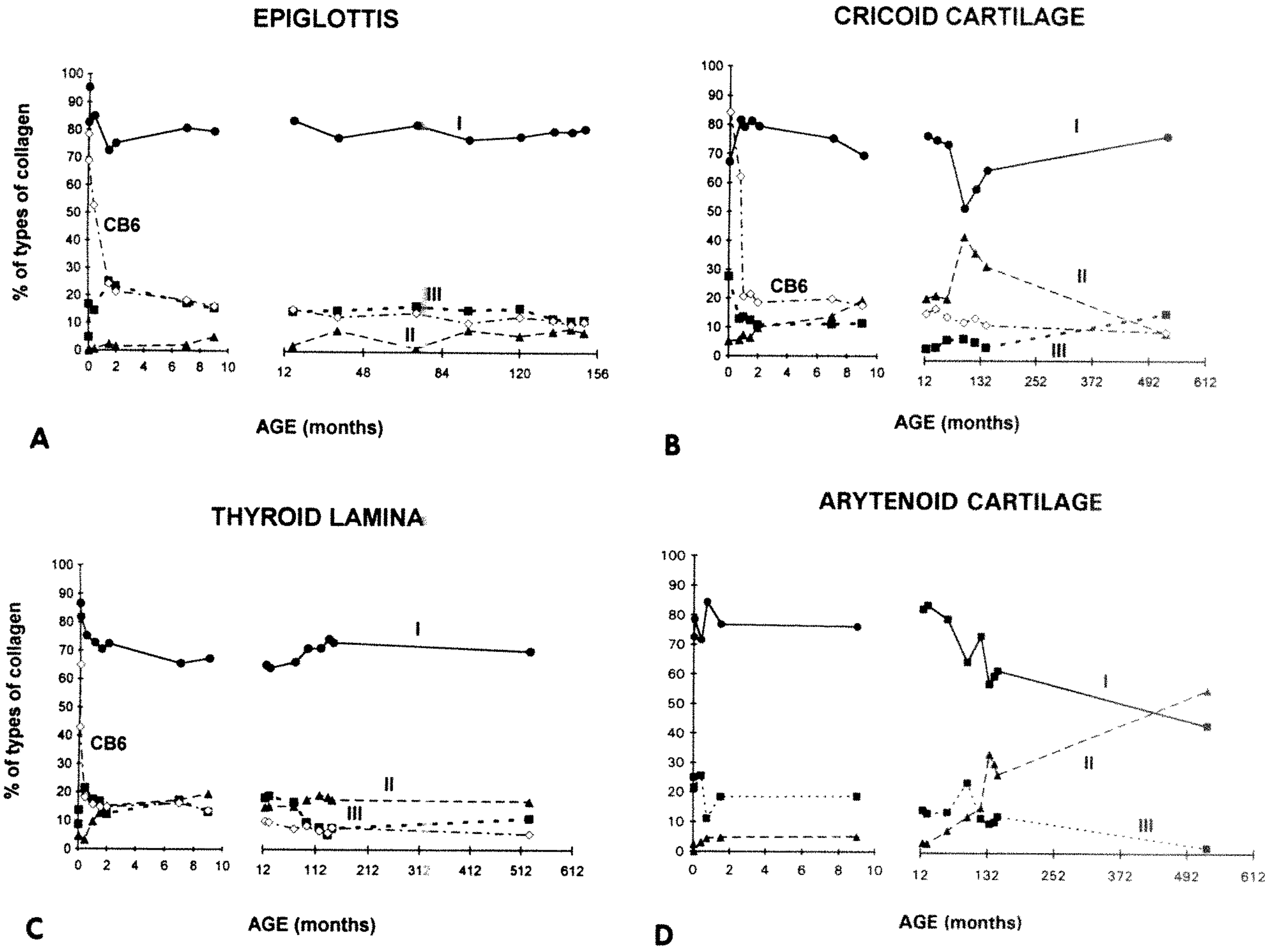
1. From the epiglottis by a transverse cut through its superior tip.
2. From the thyroid lamina at its most lateral margin.
3. From the cricoid by a sliver from the posterior lamina.
4. From the arytenoid by removal of the vocal and muscular processes.
5. From the entire length of the true vocal cord.
6. From the entire length of the false vocal cord.
7. From the trachea by removing a single ring, either the first or second.
8. From the center of the body of the hyoid, when available.

The procedures leading to identification and quantification of different collagen types are described in detail in a preliminary study on selected cartilages of the developing human larynx.[2] A summary of the method is as follows: 10 to 20 mg wet weight of each tissue sample was defatted with chloroform-methanol (50/50, vol/vol), then washed with methanol to remove chloroform. The methanol was then removed by washing the tissues in saline. The tissues were extracted with 4 mol/L guanidine to remove the proteoglycans so that the remaining tissues consisted mainly of collagen and other connective tissue proteins. The guanidine was removed by washing with saline prior to cyanogen bromide (CNBr) digestion. The CNBr digestion was carried out according to Miller.[5] The proteins were labeled as described by Cheung et al[6] with tritium-labeled sodium borohydride (^{3}H-NaBH4, 9.5 Ci/mol, obtained from Amersham, Arlington Heights, Ill) suspended in 0.2 to 0.5 mL sequenal grade dimethylformamide (obtained from Pierce Chemical Company, Rockford, Ill). The samples were desalted on a BioRad P-2 gel filtration column, and the void volume peaks containing the radioactive peptides were collected and lyophilized. The radioactively labeled CNBr peptides were subjected to overnight reduction in the presence of 25% mercaptoethanol in 0.1 mol/L ammonium carbonate. The samples were diluted with a fourfold volume of water. The mercaptoethanol was removed by desalting, and the diluted samples were placed on a P-2 column. The 2-dimensional (2-D) mapping (isoelectric focusing gel in the first dimension and sodium dodecyl sulfate gel electrophoresis in the second dimension) of the ^{3}H-labeled CNBr peptides was carried out according to Benya.[7] The fluorographs from the 2-D maps were developed in a Kodak integrator X-omatic developer and quantified by a Bioimage Visage-60 2-D densitometer.

RESULTS

The distribution of collagen types I, II, and III was analyzed by 2-D CNBr peptide mapping in the various components of the larynx from humans ranging in age from 1 day to 44 years. While 28 specimens were studied, only 17 age groups were reported, since many were of similar age. In those instances, the results were averaged. Also included in this study were the results of a preliminary study on selected cartilages of the larynx up to 5 years 10 months.[2] The results are related to age only, with no reference to the sex of the patient. In a future study, the sex-related changes will be evaluated.

Epiglottis. The changes in the distribution of collagen types I, II, and III are shown in the Figure, A. The epiglottis contains approximately 75% type I collagen in specimens ranging from ages 2 months to 15 years. The specimen of the epiglottis in the 44-year-old was not available. Very little type II collagen is found within the epiglottis until 6 months of age, but it increases to 8% as the larynx matures.


EPIGLOTTIS

CRICOID CARTILAGE

THYROID LAMINA

ARYTENOID CARTILAGE

Distribution of collagen types and non–cross-linked C-terminal CNBr peptide of $\alpha 1$(I) chain of type I collagen. Circles — type I collagen, triangles — type II, squares — type III, diamonds — CB6-$\alpha 1$(I). A) Epiglottis. B) Cricoid cartilage. C) Thyroid lamina. D) Arytenoid cartilage. (Continued on next page.)

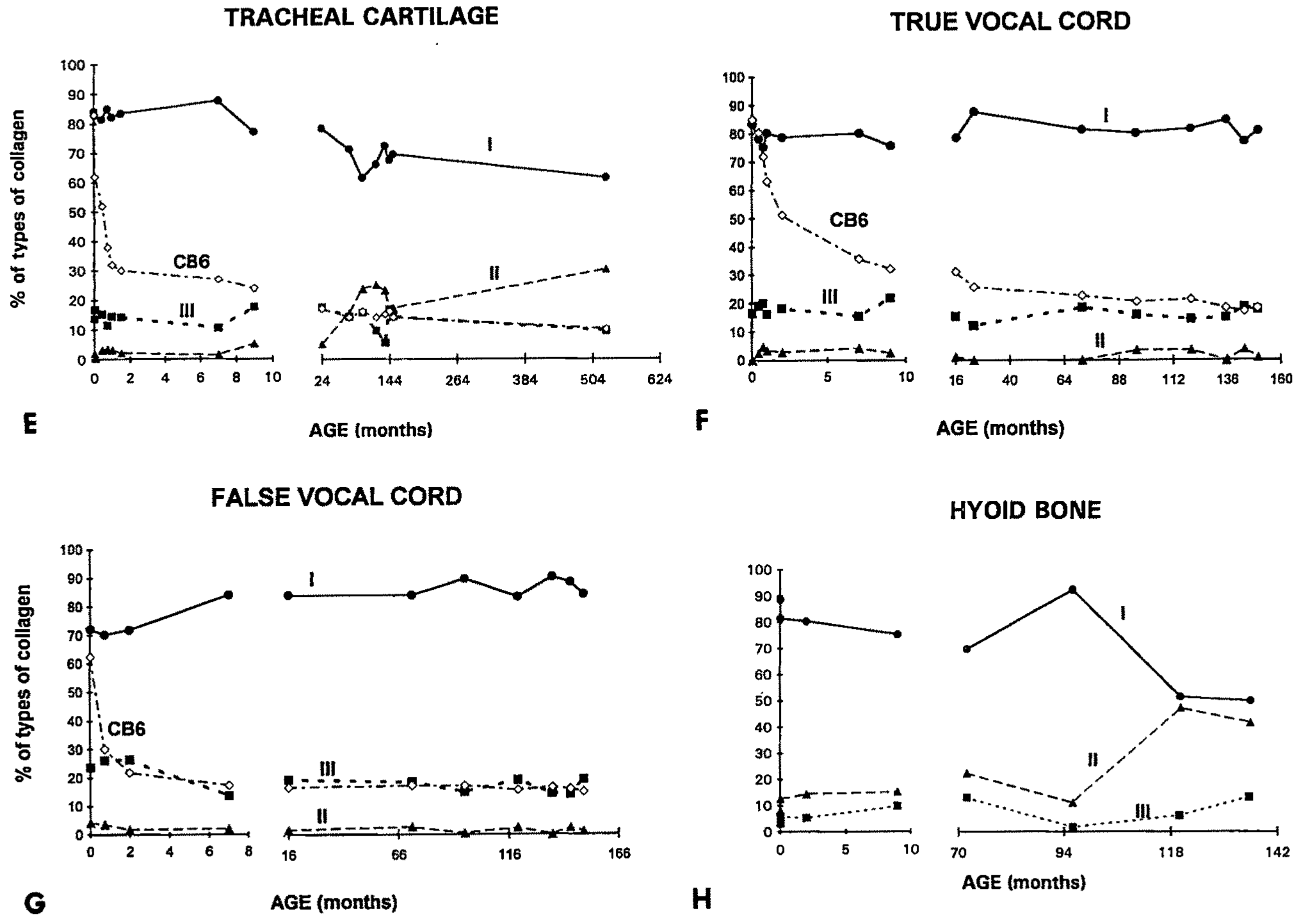
Cricoid Cartilage. The distribution of different collagens in the cricoid cartilage is shown in the Figure, B. Type I collagen increases from less than 70% to 80% during the first month of life, and then slowly decreases to 70% at 10 months of age. Type II collagen increases steadily from 5% to 20% during the first year of life. A significant shift in the distribution of type I and type II collagens occurs between the ages of 6 and 11 years, when a large increase of type II collagen (up to 45%) is observed. However, this level drops to less than 10% at age 44 years. Type I collagen decreases from 30% to 10% during the first month of life. The level of type III collagen decreases to less than 5% at 1 year of age and increases again to 30% at age 44 years.

Thyroid Lamina. At birth the thyroid lamina contains 85% type I collagen, 10% type III collagen, and 5% type II collagen. The level of type I collagen decreases rapidly to about 75% during the first month of life and then slowly decreases further to about 70% in a mature adult. Type II collagen increases rapidly to about 15% during the first 2 months and remains at this level until the larynx is fully mature. Type III collagen rises and falls rapidly to about 15% during the first month after birth and then slowly decreases to about 10% in a mature adult (see Figure, C).

Arytenoid Cartilage. Type I collagen is the major component (larger than 70%) in the arytenoid at birth (see Figure, D). Types II and III are less than 5% and 25%, respectively. Type I collagen gradually decreases to about 45% at the age of 44 years. However, type II collagen gradually increases to approximately 55% at age 44 years. Only a trace amount of type III collagen was observed in the 44-year-old larynx.

Tracheal Cartilage. The tracheal cartilage at birth is 84% type I collagen, 14% type III collagen, and less than 2% type II collagen (see Figure, E). This ratio is maintained until 6 years of age. Between the ages of 8 and 12, a significant increase of type II is accompanied by a decrease of type III. As the type II collagen continues to increase to about 30% by age 44, type I and type III collagen decrease to 60% and 10%, respectively.

True Vocal Cord. The true vocal cord at birth



(Continued) E) Tracheal cartilage. F) True vocal cord. G) False vocal cord. H) Hyoid bone.

contains about 80% type I collagen, 20% type III collagen, and an undetectable amount of type II collagen. These levels remain unchanged up to the age of 15 years. Data on the older larynx were not obtained in this study (see Figure, F).

False Vocal Cord. The composition of the collagens in the false vocal cord is quite similar to that of the true vocal cord (see Figure, G). At birth the false vocal cord is composed of 70% type I collagen, 25% type III collagen, and less than 5% type II collagen. The distribution changes to about 80% type I collagen, 20% type I collagen, and less than 2% type II collagen during the first year of life and remains at this level throughout the first 12 years of life. A specimen of this component of the larynx was not available in the 44-year-old adult.

Hyoid Bone. In the available specimens of this adjoining structure of the larynx, the distribution of the collagens is shown in the Figure, H. At birth, the level of type I collagen is 82%, the level of type II collagen is 12%, and the level of type III collagen is less than 6%. Type I collagen slowly decreases to 70%, while types II and III increase to 20% and 10%, respectively, by the age of 6 years. At age 10, the level of type I collagen decreases to 48%, and types II and III increase to 40% and 12%, respectively.

Collagen Cross-linking. Type I collagen cross-linking, measured by detecting decreased levels of intact $\alpha(1)1(-CB6)$ in most components of the larynx with the exception of the true vocal cord (see Figure, F), increases rapidly within the first month after birth, indicating that there is a rapid rate of collagen synthesis during the neonatal period. The rate of collagen synthesis is reduced significantly at the end of the first month of life.

The amount of newly synthesized collagen in the true vocal cord (see Figure, F) decreases at a slower rate than that of the other components of the larynx during the first year. At age 12, there is still a significant amount of newly synthesized collagen (which may be due to turn over for remodeling).

The decrease in newly synthesized collagen in the arytenoid cartilage (see Figure, D) and the tracheal cartilage (see Figure, E) after the first month of age continues at a slower rate during the development of the larynx.

SUMMARY

This study establishes the dynamic biologic nature of the developing and maturing human larynx. Just why these changes occur is unknown, but they stimulate speculation, since the function of the larynx, other than phonatory communication, remains constant from birth to old age. Histologically, all the major cartilages, except for the epiglottis and the medial edge and tip of the arytenoid, are composed of hyaline cartilage. Hyaline articular cartilage is known to be chiefly composed of type II collagen. Since type II collagen is actually a minor constituent of most of the laryngeal cartilages as shown by the current study, there is a discrepancy between the histology and the biochemical findings. Of the cartilaginous skeleton of the larynx, trachea, and hyoid, larger amounts of type II collagen are found only in the arytenoid, trachea, hyoid, and cricoid cartilages. The percentage of type II gradually decreases in the cricoid as the larynx matures from ages 12 to 44 years. Significant changes also occur in these four tissues between the ages of 8 and 12.

Type I collagen cross-linking increases rapidly within the first month of life in all structures except the true vocal cord. Non–cross-linked C-terminal CNBr peptide CB6 of the α1(I) chain of type I collagen indicates a rapid rate of collagen synthesis and deposition in the tissues during the neonatal period (first 30 days of life). The rapid rate of collagen synthesis slows down at the end of this period. The amount of newly synthesized collagen in the true vocal cord decreases at a slower rate than in any of the other components of the larynx during the first year of life. At age 12 there is still a significant amount of newly synthesized collagen, which may be due to a turnover that occurs with remodeling of the larynx in the adolescent.

There is a decrease in the newly synthesized collagen in the arytenoid and trachea after the first month of age, and synthesis continues at a slower rate during the developmental period of the larynx. Small but significant amounts of newly synthesized collagen are found even in the more mature larynges that were studied. This would indicate that there is a significant turnover and remodeling occurring within these tissues. It is the lack of cross-linking in the neonate that may explain why the larynx at this age shows little or no reaction to instrumentation, intubation, or endoscopic procedures.

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PLASTINATION: A NEW APPROACH TO MORPHOLOGICAL RESEARCH AND INSTRUCTION WITH EXCISED LARYNGES

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Impregnation of biologic materials with curable polymer (plastination) allows wider use of human tissue for both basic and clinical research and instruction. The aim of this study was to determine for the first time the potential of this method in the field of laryngology. A feasibility study on 54 pig larynges established a detailed methodology for larynx plastination and determined the extent of shrinkage by using computer-assisted morphometry. The process involves dehydration, saturation with an appropriate intermediate solvent, and infiltration with cured polymer in vacuo. In the main study 20 fresh, intact human larynges and 12 laryngectomy specimens were submitted to plastination. The resulting resin blocks were cut with a diamond band saw into 0.8-mm sections in the transaxial plane. The resulting specimens are dry, odorless, and durable, and do not deteriorate with time. The subtle features of soft tissue pathology are well preserved. Shrinkage of plastinated larynges is less than 10%. The complete process is accomplished within 5 weeks. Staining of sections with toluidine blue provides an enhanced contrast between different types of tissue, allowing a clear identification of tumor invasion. Plastination is considerably faster than celloidin embedding and causes minor anatomic changes. It provides durable specimens of high quality for teaching purposes. In research, it allows the investigation of all tissue components in their undisturbed context in the borderline area between gross anatomy and histology.

KEY WORDS — anatomy, embedding technique, larynx, morphometry, whole organ section.

INTRODUCTION

Whole organ sections of the larynx have contributed considerably to our knowledge of the normal and pathologic anatomy of the larynx.[1] In recent years, a number of investigations of whole organ serial sections of the larynx were conducted to determine the spread of cancer in the larynx. These studies were based on whole organ sections of selected sectors of laryngectomy specimens. The preparation of these sections involves some difficulties that are related to the complex anatomic configuration of this organ. That is, the larynx contains different tissues with a marked difference in hardness. In particular, the age-dependent ossification of the thyroid and cricoid cartilages usually requires decalcification prior to sectioning of paraffin- or celloidin-embedded larynges, if sectioning of the embedded specimen with a microtome is intended. However, decalcification requires the use of acids such as nitric or chromic acid, almost invariably causing major soft tissue damage. As prior decalcification is mandatory in the well-established techniques of celloidin and paraffin embedding, the resulting specimens are subject to unforeseeable alterations of anatomic structures and proportions.[2]

Plastination is a technique of tissue preservation that was introduced in 1979.[3] The process consists of the replacement of water and lipids in biologic tissues by curable polymers. In the meantime a wide range of different classes of polymers have been tried and tested in the fields of anatomy and pathology. The specific advantage of the plastination technique has been reported to be its excellent tissue preservation as compared to other embedding methods.[4] This potential has opened 2 major fields of interest. First, for teaching purposes, the value of plastination in providing durable specimens of high illustrative quality is well documented.[5-8] Second, in research, the technique allows the arrangement of all tissue components and their pathologic alterations to be studied in their undisturbed context. Plastination has been used to study anatomic and pathologic details in brains,[4] hearts,[9] lungs,[10] and bones.[11] The first applications to the field of head and neck surgery were reported by Bachert[12] (plastination of a nose) and Cooper et al[13] (plastination of temporal bones). Up to now there have been no reports on plastination applied to the field of laryngology.

The aim of this study was to apply the plastination method to the preparation of whole organ sections of the larynx and to determine the potential of this method in the borderline area between gross anatomy and histology with respect to cartilage (or bone), mus-

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cular, and connective tissue patterns. An effort was made to determine the degree of shrinkage and to reduce alteration of anatomic structures and proportions to a minimal and foreseeable extent.

MATERIAL AND METHODS

The larynx, with its combination of such different types of tissue as cartilage, muscles, and mucosal epithelium, is a quite difficult object for plastination. Since no records of any prior application of this technique to this organ were found, a feasibility study was conducted using pig larynges, which are easy to obtain at very low cost. The Biodur E 12 (epoxy resin), E 6 (hardener), and E 600 (accelerator) technique turned out to be the most suitable (Biodur E 6, E 12, and E 600 are supplied by Biodur GmbH, Heidelberg, Germany). To determine the degree of shrinkage caused by larynx plastination, 6 fresh larynges were dissected the same way. On 1 side of the thyroid cartilage all muscles were removed until the whole lamina was muscle-free. Then 3 points were marked with ink dots in the hyaline cartilage. On the opposite side, 3 points in the intact muscles were marked with needles. Finally, 2 points on the epiglottis, representative of elastic cartilage, were marked with ink dots. All distances between points were measured with digital vernier calipers. The measurements were repeated after treatment with formalin, acetone, and methylene chloride. Thus, we obtained data on the changes in the different tissues (muscles, hyaline, and elastic cartilage) without destruction of their native combination in the organ.

Shrinkage of areas was also evaluated. Since there is no constant area in the larynx with easy access for reliable measurements, we chose tracheal rings for this investigation. The composition of tissues in the first tracheal ring is very similar to that found in the larynx, so the results found here should be representative.

We used 11 first tracheal rings from pigs. They were projected on a computer screen via a stereo microscope with a video camera attached. The areas defined by the inner and outer circumferences were measured with a calibrated computer program. Again, measurements were repeated after treatment with formalin, acetone, and methylene chloride.

After having established a reliable routine for pig larynx plastination, we were able to transfer the technique to human larynges with no difficulty.

The procedure of plastination consists of 4 steps: fixation, dehydration, forced impregnation in a vacuum, and hardening.

For fixation, formalin was used in a concentration of 15% with an addition of 10 vol% methanol as a freeze-protecting agent in order to avoid the formation of ice crystals. Specimens were stored in this solution at 5°C for at least 5 days.

Freeze substitution in acetone at −25°C for a minimum of 3 weeks (including 4 or 5 changes of the acetone) turned out to be the best method of dehydration. Conventional ethanol dehydration is also possible, but more time-consuming, and causes major shrinkage. The final bath is in methylene chloride: both for defatting and for making sure that the specimens will sink to the bottom of the following impregnation bath without being weighted down. This effect is based on methylene chloride's high specific gravity ($\rho = 1.3$).

The central and most important step in plastination is the replacement of the methylene chloride by curable polymers. The specimen, soaked with a volatile intermediary solvent (methylene chloride), is placed into the polymer solution. A vacuum is applied, and the methylene chloride with its high vapor pressure and its low boiling point is extracted continuously in the form of gas bubbles, while the polymer solution with its low vapor pressure and its high boiling point is forced into the specimen (hence the term forced impregnation). It ends when there are no gas bubbles left, usually after 3 or 4 days. Nevertheless, we leave the specimen in the vacuum (as before at room temperature) for another 4 to 5 days in order to start the hardening gradually in the absence of any humidity. The final hardening is achieved by heat treatment at 50°C for about 1 week.

The best results were seen with a mix ratio of 100 parts Biodur E 12 to 70 parts E 6, with the addition of Biodur E 600 in a concentration of 0.15% of the total volume. This leads to a resin block of high transparency and sufficient hardness for cutting. It should be stressed that only polyethylene containers can withstand the different chemicals without disintegrating.

After hardening, the resin block should be given time to cool down slowly; then excess resin around the specimen is trimmed off with an ordinary wood saw. The rectangular block is now cut with an industrial rotating cutting machine at 2,400 rpm by a diamond-coated wheel of 30 cm diameter and a 1.2-mm cutting width. Thus, 25 to 30 slices 0.8 mm thick were obtained from every larynx.

Finally, these slices are polished with fine emery paper and polish compound like that used for metal. By this means the slices' surface is smoothed, but their transparency is still quite poor. This changes dramatically after embedding the specimen on a toluene-based liquid medium, as used in microscopy,

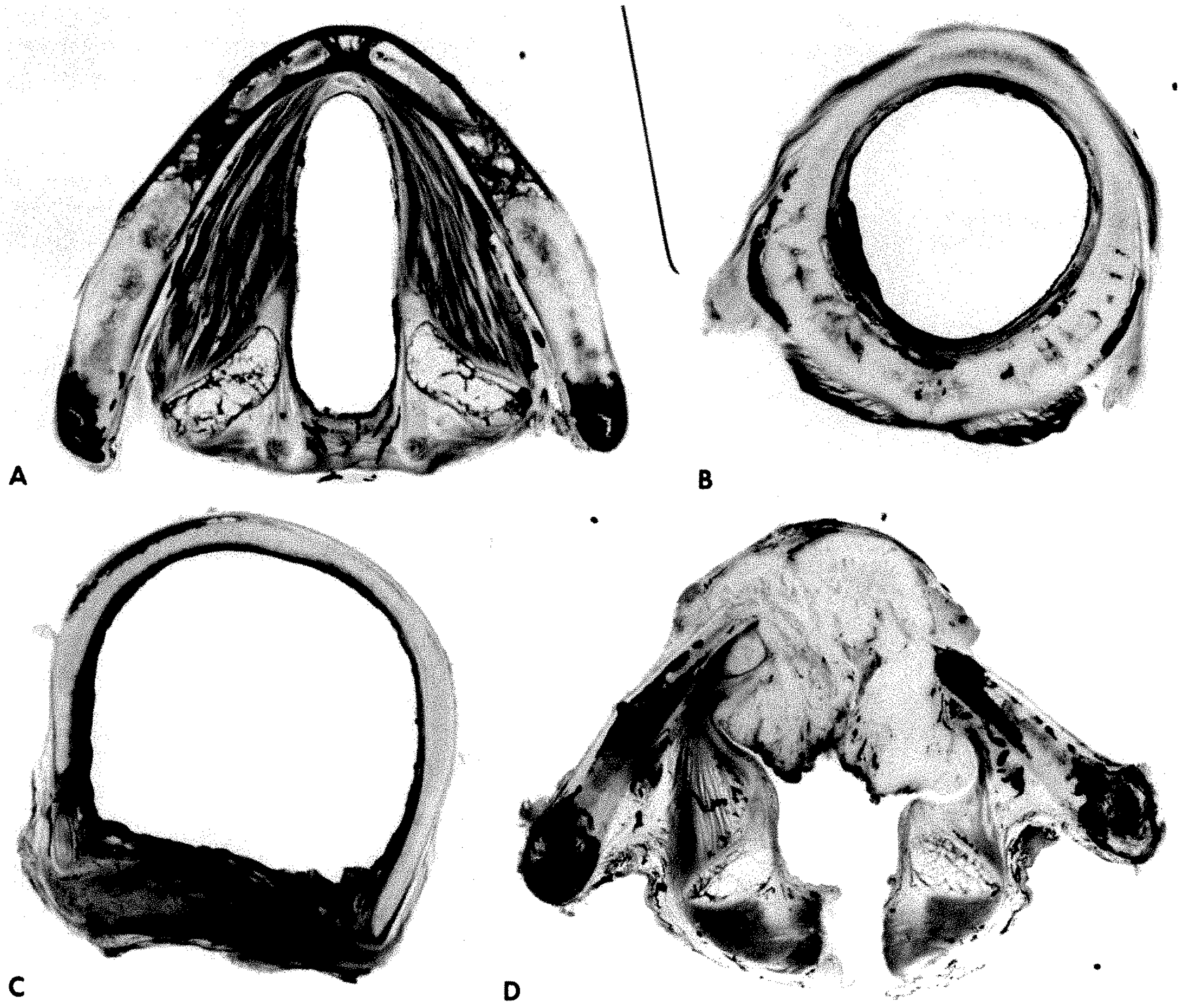


Fig 1. Plastinated human larynges. A) Glottic area in horizontal plane. B) Subglottic area in horizontal plane. C) First tracheal ring in horizontal plane. D) Laryngectomy specimen. Tumor of anterior commissure.

between 2 object slides. After several hours the liquid medium has hardened. Now the durable, odorless, dry, and very transparent specimens are ready for further investigations.

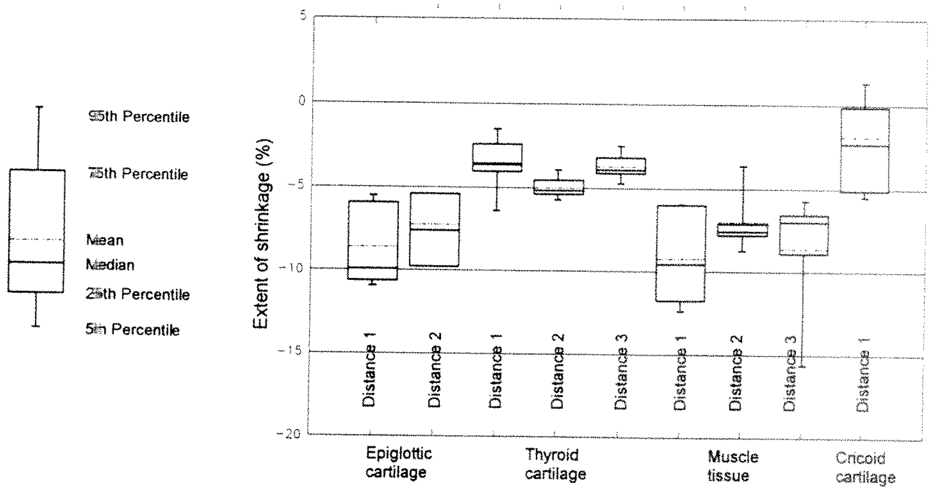
Figure 1 shows unstained specimens with nevertheless sufficient contrast. If further contrast enhancement is required, a variety of staining methods are available. An effective and simple technique is the use of toluidine blue. The specimen's surface is melted on a hot plate for a few seconds. Toluidine blue is added and rinsed off with tap water after a short time. The histologic assessment of specimens treated this way is considerably easier, but was not systematically investigated in this study.

Another approach to staining is prior deplastination. After removing the polymer, which can be accomplished with a 30% solution of sodium methylate, all standard staining techniques used in common histology can be applied. Seibold et al[11] have provided a detailed description of this laborious process.

RESULTS

The specimens resulting from the plastination technique are of high transparency. Figure 1A-C shows plastinated horizontal sections of the glottic area, the subglottic area, and the first tracheal ring. The slices were produced from the larynx of a 50-year-old man. The cause of death was a cardiac infarction, and there was no known disorder of the upper airways. Figure 1D shows a plastinated section from a laryngectomy specimen. The size and spread of the tumor of the anterior commissure can be made out clearly.

The results of the investigations on tissue shrinkage suggest that the process of plastination can reduce shrinkage to a tolerable minimum.



In the linear distances we found an average shrinkage of –3.6% for hyaline cartilage, –7.2% for muscles, and –6.6% for elastic cartilage. The major part of the shrinkage was caused by acetone freeze substitution in all cases. The spread of data with further statistical details is shown in Fig 2.

The data of the investigation of the change in the lumina of the first tracheal rings are more complex. The results show an average shrinkage of –19% for the areas defined by the outer circumference. However, the areas defined by the inner circumference increased by an average of +5%. Figure 3 demonstrates the detailed statistical results.

To summarize the findings, it can be said that the linear distances do not shrink more than 10% on any tissues. In regard to area, the differences are greater and the behavior is less predictable. Depending on the location, shrinkage of up to –23% is possible, as well as an increase in size of up to +15%.

DISCUSSION

Leroux-Robert[14] was the first to produce serial sections of whole larynges for microscopic investigation. Owing to their thickness, these sections did not lend themselves to the usual methods of staining. Tucker[15] succeeded for the first time in producing whole organ sections of high illustrative quality by establishing the use of celloidin for embedding. Others[16,17] adopted and improved this method, which is at present the technique most widely used in the United States. Kirchner[1] systematically investigated the patterns by which laryngeal cancers spread from one site in the larynx or hypopharynx to another and demonstrated the fibroelastic membranes and ligaments that divide the larynx into compartments. These observations had a substantial bearing on the development of the concept of partial laryngectomy for treatment of the early stages of laryngeal carcinoma. They also contributed new information to clinical staging of laryngeal carcinoma and to the interpretation of the findings of computed tomography and magnetic resonance imaging scans of the larynx. The work of Kirchner[1] has thus established whole organ serial sections as a major laboratory instrument in the field of anatomic and pathologic laryngeal research. These investigations were based on celloidin-embedded specimens. The disadvantages of this method of preparation lie in the very long time required (up to 10 months) and in the section thickness of 25 mm, which sets a limit to the histologic assessment.

The technique most frequently applied in Europe uses paraffin for embedding.[18] Glanz,[19] Harrison,[16] Kleinsasser,[20] Meyer-Breiting and Burkhardt,[2] and Olofsson and van Nostrand[17] conducted fundamental investigations on the intramucous and submucous spread and the 3-dimensional extension of larynx and hypopharynx carcinoma and the implications of these observations for surgical therapy. Their studies were based on the interpretation of paraffin-embedded whole organ or sector sections of the larynx and hypopharynx. These paraffin sections frequently show such artifacts as desquamation of the mucosal epithelium and fragmentation, due to the mandatory decalcification.[21] A variation of this method consists of cutting the larynx into several smaller sectors before processing. In this way handling is made easier and less artifact is produced.[19]

It is not the aim of this study to establish the plastination method as a superior embedding technique that has advantages over celloidin- or paraffin-embedding techniques in general. Plastination offers a variety of specific advantages and disadvantages. The advantages of plastination can be summarized as follows.

1. The comparative ease of handling and the need for little in the way of laboratory equipment or man-

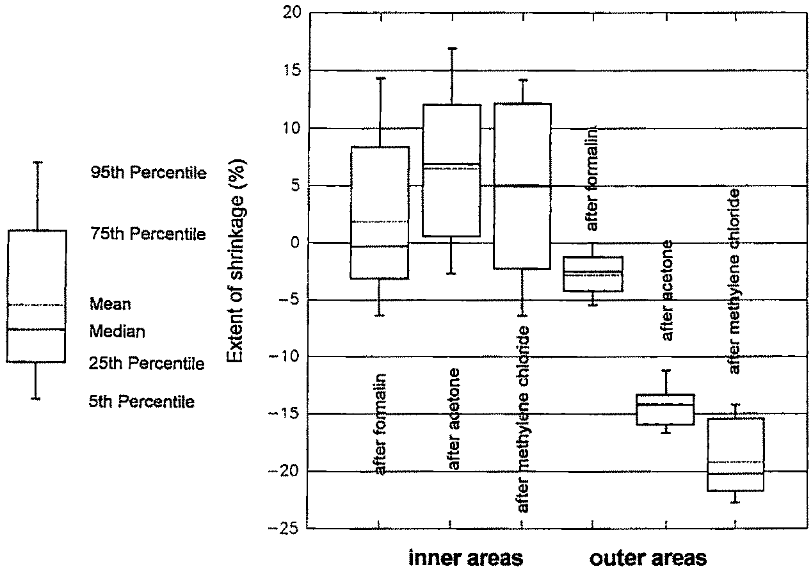


Fig 3. Shrinkage data for lumina of first tracheal rings. Areas defined by inner and outer circumference.

power support the wider use of whole organ serial sections in laryngeal research.

2. Because of the superior overview, slice thickness, transparency, and close preservation of the natural colors, the view of the borderline area between gross anatomy and histology is excellent.

3. The resulting specimens are dry, odorless, durable, and suitable for teaching.

4. Because of the preservation of natural colors, staining is usually not necessary. However, a wide variety of staining methods for special purposes are available.

5. Decalcification is not mandatory. The process of plastination therefore leads to superior tissue preservation. The regions of interest appear in their undisturbed anatomic context.

6. The alteration of anatomic proportions and shrinkage of tissues in the larynx have been documented to be minor.

The specific disadvantages of plastination are the following.

1. Histologic investigation of the obtained slices is so far not possible because of the relative thickness of the sections.

2. The cutting width of the cutting machine used in this study is 1.2 mm, resulting in a loss of material of exactly that thickness in the preparation of every section.

3. With a mean time for processing varying from 5 to 8 weeks, plastination is considerably faster than celloidin embedding, but more time-consuming than standard paraffin embedding.

However, it should be added that the method of plastination also allows the production of very thin slices, even in bony material. Seibold et al[11] reported the use of plastination for bone histology. By using sophisticated cutting equipment, sections 5 μm thick could be achieved.

To conclude, plastination is a method of tissue preservation that has demonstrated its capacity in different fields of anatomic and pathologic research and instruction. This study confirms for the first time the feasibility and potential value of the plastination method for morphological studies in laryngology. Because of its superior illustrative quality and optimal preservation of the embedded tissues, plastination may become a promising research tool in head and neck pathology and anatomy. Additionally, the dry and odorless specimens are useful devices for teaching the complex anatomy of the human larynx.

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THE WORLD HEALTH ORGANIZATION'S REVISED CLASSIFICATION OF TUMOURS OF THE LARYNX, HYPOPHARYNX, AND TRACHEA

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A second edition of the *Histological Typing of Upper Respiratory Tract Tumours* in the WHO series *International Histological Classification of Tumours* was published in 1991. The new edition has been entitled *Histological Typing of Tumours of the Upper Respiratory Tract and Ear*. The task of revising the first edition, which was published in 1978, was undertaken at the WHO Center for Upper Respiratory Tract Tumours by K. Shanmugaratnam in collaboration with L. H. Sobin and pathologists in 8 countries. Several tumour types have been added to the classification, and some have been redefined in light of current knowledge. This presentation outlines the changes in the revised WHO classification as regards tumours of the larynx, hypopharynx, and trachea and discusses the grounds for said revisions.

KEY WORDS — hypopharynx, larynx, trachea, World Health Organization tumour classification.

Tumour classification is of considerable importance, and numerous attempts have been made to correlate the type of a tumour with its biologic behavior. A distinction can be made between classifications based on clinical findings and those based on the microscopic features of tumours. The TNM system gives a coded description of the anatomic extent of neoplastic disease. The 2 most commonly applied versions of the TNM system are those of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), which have now been effectively unified.[1,2]

In biologic terms, a neoplasm can be defined as abnormally functioning tissue in an organism, whose excessive growth is generated by a clone or clones of cells that have acquired genetic or epigenetic change and escaped from normal tissue control, and whose abnormal behavior is dictated by the functional level of that control expressed through the lineage of clone(s).[3]

To provide internationally acceptable criteria for the histologic diagnosis of tumours, the World Health Organization (WHO) published its *International Histological Classification of Tumours*, which is an illustrated, multivolume series containing definitions of tumour types and a proposed nomenclature.

The first edition of the WHO *Histological Typing of Upper Respiratory Tract Tumours* was published in 1978.[4] This classification naturally also included neoplasms of the larynx, hypopharynx, and trachea, based on knowledge of tumours and tumourlike lesions available at the time, and its nomenclature was widely adopted. The considerable advances in histopathology, immunohistochemistry, and electron microscopy of the last 15 years have led to the need for a reappraisal of the WHO classification.

For this purpose, an international group of experts was established, comprising K. Shanmugaratnam (Singapore), L. H. Sobin (United States), L. Barnes (United States), A. Cardesa (Spain), A. Ferlito (Italy), I. Friedmann (England), D. K. Heffner (United States), H. B. Hellquist (Sweden), V. J. Hyams (United States), G. R. F. Krueger (Germany), C. Micheau (France), and A. Nascimento (Brazil). Several of these experts met in Dublin in 1988, and the amply illustrated, revised classification was published in 1991.[5] This article summarizes the major changes in the new classification and provides explanations or commentary on the alterations.

Like its predecessor, the new classification (Table 1) is based on histologic features observable with conventional light microscopy. The adjuvant value of ancillary techniques, such as immunocytochemistry and electron microscopy, is still limited, but they have been helpful in specific circumstances (such as in neuroendocrine neoplasms). The second edition is more complete and detailed than the previous version. In fact, 32 new entities have been included (Table 2), 13 of which are malignant epithelial neoplasms, and several of these are the counterparts of malignant neoplasms of the major salivary glands (Table 3).

The lymphoepithelial carcinoma is a particular type that is histologically identical to the lymphoepithelial undifferentiated carcinoma of the nasopharynx.

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TABLE 1. HISTOLOGICAL TYPING OF TUMOURS OF LARYNX, HYPOPHARYNX, AND TRACHEA

1	**Epithelial tumours and precancerous lesions**	
1.1	*Benign*	
1.1.1	Papilloma	8052/0
	Papillomatosis	8060/0
1.1.2	Pleomorphic adenoma	8940/0
1.1.3	Basal cell (basaloid) adenoma	8140/0
1.2	*Dysplasia and carcinoma in situ*	
1.2.1	Squamous cell dysplasia	74009
1.2.1.1	Mild dysplasia	74006
1.2.1.2	Moderate dysplasia	74007
1.2.1.3	Severe dysplasia	74008
1.2.2	Carcinoma in situ	8070/2
1.3	*Malignant*	
1.3.1	Squamous cell carcinoma	8070/3
1.3.2	Verrucous squamous cell carcinoma	8051/3
1.3.3	Spindle cell carcinoma	8074/3
1.3.4	Adenoid squamous cell carcinoma	8075/3
1.3.5	Basaloid squamous cell carcinoma	8094/3
1.3.6	Adenocarcinoma	8140/3
1.3.7	Acinic cell carcinoma	8550/3
1.3.8	Mucoepidermoid carcinoma	8430/3
1.3.9	Adenoid cystic carcinoma	8200/3
1.3.10	Carcinoma in pleomorphic adenoma	8941/3
1.3.11	Epithelial-myoepithelial carcinoma	8562/3
1.3.12	Clear cell carcinoma	8310/3
1.3.13	Adenosquamous carcinoma	8560/3
1.3.14	Giant cell carcinoma	8031/3
1.3.15	Salivary duct carcinoma	8500/3
1.3.16	Carcinoid tumour	8240/3
1.3.17	Atypical carcinoid tumour	8246/3
1.3.18	Small cell carcinoma	8041/3
1.3.19	Lymphoepithelial carcinoma	8082/3
2	**Soft tissue tumours**	
2.1	*Benign*	
2.1.1	Aggressive fibromatosis	8821/1
2.1.2	Myxoma	8840/0
2.1.3	Fibrous histiocytoma	8830/0
2.1.4	Lipoma	8850/0
2.1.5	Leiomyoma	8890/0
2.1.6	Rhabdomyoma	8900/0
2.1.7	Hemangioma	9120/0
2.1.8	Hemangiopericytoma	9150/1
2.1.9	Lymphangioma	9170/0
2.1.10	Neurilemmoma	9560/0
2.1.11	Neurofibroma	9540/0
2.1.12	Granular cell tumour	9580/0
2.1.13	Paraganglioma	8693/1
2.2	*Malignant*	
2.2.1	Fibrosarcoma	8810/3
2.2.2	Malignant fibrous histiocytoma	8830/3
2.2.3	Liposarcoma	8850/3
2.2.4	Leiomyosarcoma	8890/3
2.2.5	Rhabdomyosarcoma	8900/3
2.2.6	Angiosarcoma	9120/3
2.2.7	Kaposi's sarcoma	9140/3
2.2.8	Malignant hemangiopericytoma	9150/3
2.2.9	Malignant nerve sheath tumour	9560/3
2.2.10	Alveolar soft part sarcoma	9581/3
2.2.11	Synovial sarcoma	9040/3
2.2.12	Ewing's sarcoma	9260/3
3	**Tumours of bone and cartilage**	
3.1	*Benign*	
3.1.1	Chondroma	9220/0
3.2	*Malignant*	
3.2.1	Chondrosarcoma	9220/3
3.2.2	Osteosarcoma	9180/3
4	**Malignant lymphomas**	9590/3
5	**Miscellaneous tumours**	
5.1	*Benign*	
5.1.1	Mature teratoma	9080/0
5.2	*Malignant*	
5.2.1	Malignant melanoma	8720/3
5.2.2	Malignant germ cell tumours	
6	**Secondary tumours**	
7	**Unclassified tumours**	
8	**Tumourlike lesions**	
8.1	Cysts	33400
8.2	Hamartoma	75500
8.3	Heterotopic thyroid tissue	26100
8.4	Vocal cord nodule and polyp	76800
8.5	Fibroinflammatory pseudotumour	76820
8.6	Infective granulomas	44000
8.7	Wegener's granulomatosis	44780
8.8	Pseudoepitheliomatous hyperplasia	72090
8.9	Squamous cell hyperplasia	72000
8.10	Keratosis	72600
8.11	Necrotizing sialometaplasia	73221
8.12	Oncocytic metaplasia and hyperplasia	73050
8.13	Granuloma pyogenicum	44440
8.14	Intubation granuloma	44450
	Contact ulcer	10540
8.15	Elastic cartilage metaplasia	73600
8.16	Tracheopathia osteochondroplastica	73400
8.17	Relapsing polychondritis	43000
8.18	Aneurysmal bone cyst	33640
8.19	Lymphoid hyperplasia	72200
8.20	Plasma cell granuloma	43060
8.21	Malakoplakia	43180
8.22	Langerhans' cell histiocytosis	77910
8.23	Rosai-Dorfman disease	77940
8.24	Amyloid deposits	55100
8.25	Gouty tophi	55070
8.26	Lipoid proteinosis	55650

Morphology codes are from International Classification of Diseases for Oncology (ICD-O) and/or Systematized Nomenclature of Medicine (SNOMED).

TABLE 2. TUMOURS NEW TO REVISED WHO CLASSIFICATION

- **Epithelial tumours**
  - *Benign*
    - Pleomorphic adenoma
    - Basal cell (basaloid) adenoma
  - *Malignant*
    - Adenoid squamous cell carcinoma
    - Basaloid squamous cell carcinoma
    - Acinic cell carcinoma
    - Mucoepidermoid carcinoma
    - Carcinoma in pleomorphic adenoma
    - Epithelial-myoepithelial carcinoma
    - Clear cell carcinoma
    - Adenosquamous carcinoma
    - Giant cell carcinoma
    - Salivary duct carcinoma
    - Atypical carcinoid tumour
    - Small cell carcinoma
    - Lymphoepithelial carcinoma
- **Soft tissue tumours**
  - *Benign*
    - Aggressive fibromatosis
    - Myxoma
    - Fibrous histiocytoma
    - Hemangiopericytoma
    - Lymphangioma
  - *Malignant*
    - Malignant fibrous histiocytoma
    - Liposarcoma
    - Leiomyosarcoma
    - Malignant hemangiopericytoma
    - Malignant nerve sheath tumour
    - Alveolar soft part sarcoma
    - Synovial sarcoma
    - Ewing's sarcoma
- **Tumours of bone and cartilage**
  - *Malignant*
    - Osteosarcoma
- **Miscellaneous tumours**
  - *Benign*
    - Mature teratoma
  - *Malignant*
    - Malignant melanoma
    - Malignant germ cell tumours

WHO — World Health Organization.

TABLE 3. SALIVARY GLAND TUMOURS ADDED TO REVISED WHO CLASSIFICATION

- Acinic cell carcinoma
- Mucoepidermoid carcinoma
- Carcinoma in pleomorphic adenoma
- Epithelial-myoepithelial carcinoma
- Clear cell carcinoma
- Salivary duct carcinoma

WHO — World Health Organization.

Among the new tumours considered, the basaloid squamous cell carcinoma is a new morphological and phenotypic entity with a distinct prognostic significance, described by Wain et al in 1986.[6] This particular tumour is a carcinoma with a basaloid pattern associated with in situ and/or invasive squamous cell carcinoma. The basaloid component consists of small, crowded cells with hyperchromatic nuclei, scant cytoplasm, small cystic spaces containing material resembling mucin that stains with PAS and/or Alcian blue, foci of coagulative necrosis within the central areas of the tumour lobules, and hyalinosis. Ultrastructurally, the basaloid cells possess rare tonofilaments and various amounts of desmosomes; neurosecretory granules are noticeably absent. Immunohistochemically, the tumour shows reactivity to cytokeratin, epithelial membrane antigen, carcinoembryonic antigen, neuron-specific enolase, S-100 protein, and vimentin.

This tumour has an aggressive behavior that justifies its distinction from other neoplasms. The most difficult differential diagnosis in the pure form of basaloid carcinoma is from the solid form of adenoid cystic carcinoma and from small cell neuroendocrine carcinoma.

The previous classification's vague category "others" has been discarded, and so have certain doubtful entities such as oxyphilic adenoma (oncocytoma) (because it is not a true neoplasm) and "undifferentiated" carcinoma (because it has been attributed to a heterogeneous group of neoplasms notoriously difficult to distinguish). The application of electron microscopy, immunohistochemical methods with an ever-increasing arsenal of antibodies, and recently developed molecular biology techniques will enable more accurate identification and thus more reliable classification of neoplasms.[7]

Although the new WHO classification is more comprehensive than before, some neoplasms described in the literature have not been included[8-13] (Table 4).

Of the important group of neuroendocrine neoplasms, only carcinoid tumour and paraganglioma were listed in the earlier WHO classification; atypical carcinoid tumour and small cell neuroendocrine carcinoma have now been added. These tumours share many histologic, immunohistochemical, and electron microscopic features with the more common neuroendocrine neoplasms of the lung. The diagnosis of these neoplasms should therefore be made only after excluding the likelihood of a primary tumour arising in the lung. Atypical carcinoid tumour is not so rare in the larynx as to be a medical curiosity; it is the most common type of nonsquamous laryngeal carcinoma.[14] Small cell neuroendocrine carcinoma is

TABLE 4. NEOPLASTIC ENTITIES DESCRIBED IN LITERATURE BUT NOT INCLUDED IN REVISED WHO CLASSIFICATION

Sebaceous carcinoma
Mucoid adenocarcinoma
Malignant granular cell tumour
Malignant myoepithelioma
Malignant mesenchymoma
Laryngeal blastoma

WHO — World Health Organization.

now specifically mentioned, too, and recognized as a separate entity; prognosis for this tumour is usually poor, and the clinical course is rapidly fatal.

Hopefully, this classification will find wide acceptance among pathologists, laryngologists, radiotherapists, and oncologists, as well as epidemiologists, thereby facilitating the comparison of results in the various fields of oncology. A histologic classification of neoplasms is of the utmost importance for predicting prognosis and thus also influences the clinical management of patients.

The oncotype provides a *qualitative* diagnosis of the disease. Biologic behavior varies from one type of cancer to another, so only similar types are comparable for prognostic implications.

Survival is generally related to specific histologic types. It is common knowledge that small cell neuroendocrine carcinoma metastasizes more frequently than conventional squamous cell carcinoma, and that the latter is more malignant than verrucous squamous cell carcinoma. Each malignant tumour has its own degree of intrinsic aggressiveness. Prognosis consequently differs enormously: considering all stages of the disease, 5-year survival rates are about 60% for conventional squamous cell carcinoma of the larynx,[15] 48% for atypical carcinoid tumour,[16] and 5% for small cell neuroendocrine carcinoma.[17] Taking conventional squamous cell carcinoma as a standard for comparison, verrucous squamous cell carcinoma, most mucoepidermoid carcinomas, and typical carcinoid tumours have a more favorable prognosis, whereas small cell neuroendocrine carcinoma, basaloid squamous carcinoma, and atypical carcinoid tumours are likely to have a less favorable outcome.

Moreover, identification of the histologic type permits specific and individual tumour staging protocols. The oncotype should therefore be considered as a major guideline for decisions on treatment modalities.

In conclusion, we must first learn to accurately recognize a tumour before we can treat it most effectively.

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RESECTION OF TRACHEAL STENOSIS WITH END-TO-END ANASTOMOSIS

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We present our experience with circumferential tracheal resection with end-to-end anastomosis. Between 1985 and 1992 we performed this procedure on 19 patients with tracheal stenosis. The cause of the stenosis was related to intubation and/or tracheotomy in 78.9% of the patients. Two to 8 tracheal rings were resected and a tension-free anastomosis was achieved with mobilization techniques that were limited to suprahyoid release, peritracheal dissection, and chin-to-chest suture. Infrahyoid release and intrathoracic perihilar mobilization techniques were not used. The anastomosis success rate was 94.7%.

KEY WORDS — anastomosis, stenosis, trachea.

INTRODUCTION

With recent advances in critical care medicine, more patients who are treated for trauma and cardiorespiratory disease, as well as patients who have had major cardiac or pulmonary surgery, become intensive care unit survivors. These changes, according to Montgomery,[1] have resulted in an increased number of laryngotracheal injuries. Although the use of low-pressure, high-volume cuffed endotracheal and tracheotomy tubes has been shown to decrease the rate of tracheal stenosis,[2] the overall increase in the number of patients requiring these tubes results in a considerable number of long-term injuries. It has been repeatedly stated that circumferential resection with primary end-to-end anastomosis, when possible, should be the treatment of choice for tracheal stenosis.[2-5] This report reviews our experience with this procedure.

PATIENTS AND METHODS

We keep a registry of patients with laryngotracheal stenosis treated at our institution. Between 1985 and 1992, 110 patients were treated surgically for laryngotracheal stenosis. Of these, 19 patients had circumferential resection with end-to-end anastomosis. Excluded from this study were patients under 10 years of age, patients whose stenosis was a result of neoplasm or goiter, patients with true subglottic (cricoid) stenosis, and patients with tracheomalacia without stenosis. There were 12 males and 7 females, with a mean age of 43 years (range 14 to 66 years). Twelve patients (63.2%) had had between 1 and 8 previous conventional or laser endoscopic treatments. Plain x-ray studies, computed tomography, and endoscopic examination were performed in all patients. Magnetic resonance imaging studies, polytomography (Fig 1), and flow-volume respiratory function studies were performed in 9, 9, and 4 patients, respectively. Treatment is considered successful if the patient is asymptomatic for a minimum follow-up of 1 year and either plain x-ray studies or office flexible tracheoscopy show a patent airway.

RESULTS

Most of the patients developed stenosis secondary to endotracheal intubation and/or tracheotomy (see Table). The 1 miscellaneous case was in a patient with delayed (1 year postinjury) erosion of the trachea by a piece of shrapnel. The location of the upper limit of the stenosis was at the first tracheal ring in 4 patients, second ring in 5 patients, third to fifth ring in 6 patients, and fifth to eighth ring in 4 patients. The length of the stenosis as determined intraoperatively ranged from 1 to 8 rings. Nine patients (47.4%) had a stenosis measuring 3 or 4 rings in length. Preoperative estimation of the length of the stenosis, based on imaging studies and endoscopy, was usually accurate. The difference between preoperative and intraoperative measurements was less than 1 cm in all patients.

Six patients had a tracheotomy present at the time of surgery. In 5 of them the tracheotomy was related to the stenosis, and therefore surgery included resection of the tracheotomy site. In 1 patient it was not related to the stenosis, and therefore the tube was left in place and the patient was decannulated 10 days

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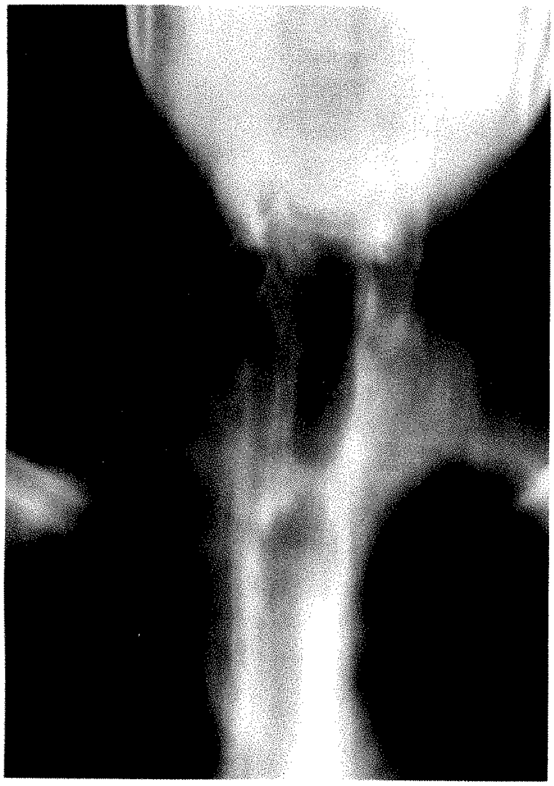

Fig 1. Tomography for diagnosis of cervical tracheal stenosis.

after surgery. Eighteen patients (94.7%) had the surgery performed through a transcervical approach. One patient, a 14-year-old girl with a 7-ring stenosis starting at the fourth tracheal ring, had modified superior sternotomy. Eighteen patients (94.7%) had complete circumferential resection of the stenotic segment. One patient (5.3%) with a stenotic segment of 1 ring had resection of 75% of the circumference. The posterior wall was left intact and created only a minimal intraluminal buckling that did not result in any significant obstruction.

All patients had peritracheal, mainly pretracheal, dissection and mobilization. Fifteen patients (78.9%) had suprahyoid laryngeal release. Seventeen patients (89.5%) had extreme flexion with a chin-to-chest suture. No other release procedures were done.

Sixteen patients (84.2%) were extubated at the termination of the procedure, on the operating room table. Two patients were extubated within the first 36 hours because of late finish time. One patient was left with a tracheotomy tube in place. Of the 16 patients who were extubated immediately, 1 patient had to be reintubated a few hours later. It was eventually found that the patient had 2 stenotic areas: a tracheal stenosis at the third and fourth rings that was resected, and subglottic stenosis that was less significant preoperatively, but became edematous immediately after surgery. During reoperation for subglottic stenosis repair, the tracheal resection and anastomosis site was found to be patent.

CAUSES OF TRACHEAL STENOSIS

Causes	*No. of Pts*
Intubation	5
Tracheotomy	5
Intubation and/or tracheotomy	5
External tracheal trauma	3
Miscellaneous	1

Two patients had additional surgery. One patient had endoscopic removal of granulation tissue at the anastomosis line 6 weeks after the resection. The problem did not recur and he is currently asymptomatic. The second patient had a sternocleidomastoid myoperiosteal flap[6] for reconstruction of the subglottic area, 6 weeks after resection of tracheal stenosis at a different site.

One anastomosis failed. The patient developed significant granulation tissue at the anastomosis line and required tracheotomy. The patient was scheduled for endoscopic management with possible resection, but he moved out of state and was lost to our follow-up. Thus, the anastomosis success rate was 94.7%. Taking into account the patient with 2 stenotic sites, the total success rate (asymptomatic patient with patent airway) was 89.5%.

No other major complications occurred. One patient developed superficial wound infection that was treated successfully with local wound care. All patients were able to tolerate oral intake by the second or third postoperative day. There were no cases of postoperative pneumonia or pneumothorax. Iatrogenic vocal cord paralysis was not seen in this series. (Two patients who had external tracheal trauma had preoperative unilateral vocal cord paralysis.)

SURGICAL TECHNIQUE

Patients without tracheotomy are intubated nasotracheally. A low collar incision is made. Since the stenosis in patients with tracheotomy present at the time of surgery is most commonly (5 of 6 patients in our series) related to the tracheotomy itself, the incision will include the tracheotomy site and the entire tracheotomy tract will be eventually removed with the resected trachea. In the rare case of a stenosis not related to an existing tracheotomy (1 patient in our series), the cervical incision will be made at least 2 cm away from the tracheotomy and the patient will not be decannulated at the time of surgery. After elevating subplatysmal flaps and retracting the strap muscles laterally, the trachea is exposed in the midline. If

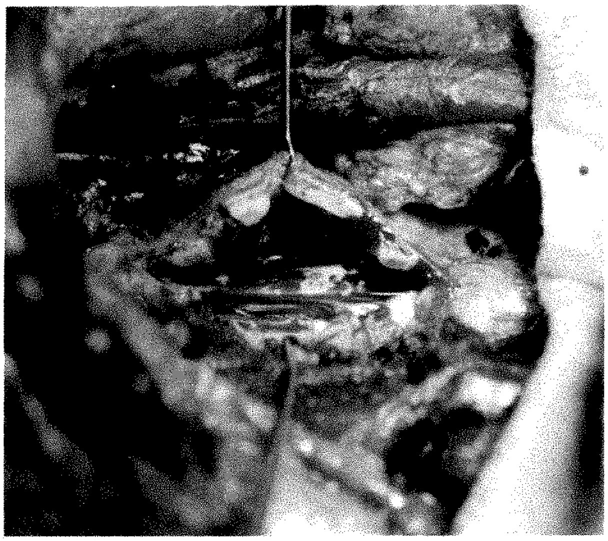

Fig 2. Vertical tracheal incision is made first. Only after length of stenosis has been determined are horizontal circumferential incisions made.

needed, the thyroid isthmus is transected and the lobes are retracted laterally.

If a tracheotomy is present, the trachea is incised vertically through the stoma, both superiorly and inferiorly, until normal mucosa is seen. If a tracheotomy is not present, the stenotic area is usually easy to identify because of external changes. Rarely, the surgeon may not be able to identify the stenotic area easily. In this case the incision is made based on measurements from the cricoid cartilage made during previous diagnostic endoscopy. Endoscopy may also be performed simultaneously during tracheal resection, and the stenotic area may be identified by pushing the tip of the endoscope anteriorly and palpating it in the surgical field. Once the stenotic area has been identified, a vertical midline incision is made and extended superiorly and inferiorly until normal mucosa is seen (Fig 2).

Once normal mucosa is seen inferiorly, horizontal incisions are made. A second ventilating system with a flexible endotracheal tube is brought to the field, and the distal trachea is intubated. The orotracheal tube is pulled out until the tip of the tube is above the proximal resection line. Both superior and inferior circumferential resection lines are now completed. The resected specimen is grasped and pulled, and dissection is carried around it. Dissection is performed close to the tracheal wall and no effort is made to identify the recurrent laryngeal nerves. Posteriorly, the stenotic segment is separated from the esophagus by means of both blunt and sharp dissection. If the distal resection line is below the thoracic inlet, blunt, pretracheal dissection toward the carina is done before removal of the stenotic segment. In this case, a 2-0 prolypropylene suture is placed horizontally through the third ring below the resection line to aid with pulling the distal segment superiorly. Once the stenotic segment is removed, dissection is also carried out between the trachea and the esophagus, but only for a short segment. In any event, no dissection and mobilization are performed on the lateral aspects of the distal trachea.

The superior subplatysmal flap is now elevated superior to the hyoid bone. The hyoid bone is identified, and sharp suprahyoid horizontal dissection is begun. The suprahyoid muscles are transected in between the attachments of the digastric muscles. Dissection is continued deep through the entire preepiglottic space. With heavy scissors, the body of the hyoid bone is separated from the greater cornua. The muscles and ligaments attached to the lesser cornua are also transected, or as suggested by Montgomery,[1] the lesser cornua themselves are transected and separated from the body of the hyoid. On completion of this maneuver and after removal of the shoulder support, the anastomosis is now ready to be done. We do not use the technique of intercartilaginous incisions for gaining additional tracheal length. The surgeon should not be concerned about a small gap that may still be present at this point, as all tension will be eventually relieved by the extreme flexion applied at the end of the procedure.

Although the anastomosis in most of our early cases was performed with polyester fiber (Tevdek) sutures, it seems that polypropylene (Prolene), polyglactin (Vicryl), and polyglycolic acid (Dexon) sutures were used by us and others with the same good results.[1-4,7] We use 4-0 sutures. The posterior trachea is anastomosed first. Sutures are placed submucosally by starting from the posterior midline and moving laterally on both sides. Once all posterior sutures are placed, they are tied simultaneously from both sides. Next, the lateral parts of the anastomosis are done by the same technique. The endotracheal tube is now removed from the distal trachea and the nasotracheal tube is passed distally, bridging the gap. The anastomosis is now completed anteriorly. Three to 4 heavier sutures (2-0) are placed submucosally around the second ring superior and second ring inferior to the anastomosis and are tied in order to achieve a tension-free anastomosis line. Two Penrose drains are placed in the wound. One is at the anastomosis and superior mediastinum, and the other is at the hyoid level. The wound is closed in layers. A 2-0 nylon suture is placed between the chin and the anterior chest wall and tied to achieve maximum neck flexion (Fig 3).

We make all efforts to extubate the patients in the

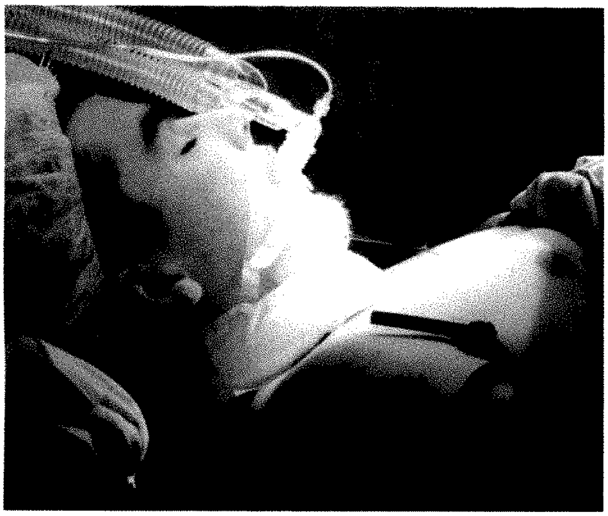

Fig 3. Chin-to-chest suture for flexion. Maximum flexion may be achieved by tightening suture and bringing chin closer to chest.

operating room. This was performed successfully in 84.2% of our patients. Two patients were extubated within the first 36 hours postoperatively, and 1 patient remained with a tracheotomy tube that was not related to the anastomosis line. The trachea should be suctioned vigorously before the tube is removed.

There is no need for a feeding tube; all of our patients were able to tolerate oral intake on the second postoperative day. The chin-to-chest suture is removed in 10 to 14 days. For follow-up evaluation of airway patency we use either plain films or office flexible laryngoscopy and tracheoscopy with a small-caliber laryngoscope with a suction port that is used to instill local anesthetic into the larynx to facilitate the procedure.

DISCUSSION

Our study confirms the previous observations that the results of complete circumferential tracheal resection with end-to-end anastomosis are favorable and a cure should be expected in the majority of cases.[2,3,5,7] These findings bring up the philosophic question of what is "conservative" management and what is "aggressive" management of tracheal stenosis. Does "conservative" mean an endoscopic and not open surgical procedure? Or should it mean better chances for cure after the first attempt?

Tracheal stenosis is a process that begins with local inflammatory reaction and ends in complete mature stenosis. This process has been divided into 3 stages for clarity. The first stage is the granulation stage. Limited scarring with some inflammatory process still present characterizes the second stage. Complete, mature stenosis is found in the third stage. On the basis of our experience and the results of this study, we currently limit the use of conventional as well as laser endoscopic treatment to the first stage only.

Plain airway films and endoscopic assessment remain the mainstay of preoperative workup.[1,7,8] Fluoroscopy is useful in cases of suspected or proven tracheomalacia.[7] Although a computed tomographic scan was performed in all of our patients, it did not add much to the information needed for the tracheal resection procedure. The goal of the preoperative workup is to determine the location, characteristics (inflammation, granulation, maturation), length, and circumference of the stenosis.[2,8] This information is critical in determining the approach and the need for additional mobilization procedures.[4] The patient's general condition and especially his or her neurologic and pulmonary status are extremely important. The patient's ability to swallow, to avoid aspiration, and to produce a strong cough should be assessed. It has been shown that old age, short stature, a history of previous resection, and the presence of a tracheotomy may result in a less favorable outcome.[5] However, it seems that the overall high success rate of the procedure makes these other factors less critical.

The issue of when and which mobilization technique to use for gaining additional tracheal length in resection cases has always been an important part in the discussion of this procedure.[1,3-5,8] The different mobilization techniques include extreme flexion, suprahyoid release, infrahyoid release, inferior constrictor release, peritracheal mobilization, intercartilaginous incisions, dissection and mobilization of the right hilum, release of the inferior pulmonary ligament, dissection of the pulmonary vasculature, and transection and reimplantation of the left main stem bronchus.[4,5] We have found that the use of extreme flexion, supralaryngeal release, and peritracheal mobilization was sufficient to achieve satisfactory tracheal length and tension-free anastomosis in all of our cases. As for the type of the supralaryngeal release, a recent study of patients who had combined infrahyoid and inferior constrictor release showed that 20% of the patients had prolonged postoperative dysphagia.[3] In our study, suprahyoid release, while providing good inferior mobilization of the proximal segment, did not result in dysphagia. Also, suprahyoid release does not put the superior laryngeal neurovascular pedicle at risk. Grillo[7] has also recommended suprahyoid release. Because of these findings, we do not use a nasogastric tube after surgery.[1-4]

The timing of extubation is controversial. Biller and Munier[3] believe that leaving the patient intubated for 48 hours allows the suture line to become airtight before it is exposed to positive intratracheal pressure. Others believe that any possible endotracheal tube injury to the anastomosis or to a different segment in the trachea should be avoided in patients with a history of reaction to the tube or its cuff. We did not have problems with immediate extubation of our patients.

CONCLUSIONS

Nineteen patients with tracheal stenosis ranging from 1 to 8 rings in length were managed by complete circumferential tracheal resection and end-to-end anastomosis. For tracheal mobilization, suprahyoid release and extreme flexion were used. Only 1 patient has redeveloped stenosis. There were no major complications and no compromise of swallowing. This experience suggests that the procedure is relatively safe and effective.

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CRITICAL CARE MEDICINE: A COMPREHENSIVE REVIEW AND UPDATE

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MICROENDOSCOPIC LASER DIVERTICULOTOMY FOR HYPOPHARYNGEAL DIVERTICULUM

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Progressive dysphagia due to a pharyngeal pouch eventually requires surgical treatment. Thirty-four patients treated by laser diverticulotomy in a 6-year period were reviewed for age, length of hospitalization, associated medical problems, postoperative course, and results. The operative technique is described in detail, and a new, slimmer diverticuloscope is introduced. Microendoscopic laser diverticulotomy offers excellent visualization by means of the operating microscope together with a double-lipped diverticuloscope and is a minimally invasive, relatively simple, controlled procedure with proven, predictable results and few complications. It can be recommended as the treatment of choice for patients of all ages, whether the pouch is large or small.

KEY WORDS — diverticuloscope, laser, pharyngeal diverticulum.

INTRODUCTION

The upper esophageal sphincter (UES) at the transition from hypopharynx to esophagus is normally closed by a resting muscular tone and is opened during swallowing by relaxation of the muscle fibers, together with cranial displacement of the larynx creating a negative pressure.[1,2] An explanation for the cause of hypopharyngeal (Zenker's) diverticulum assumes that a combination of weakness of Killian's triangle and powerful contraction of the UES causes mucosal herniation and eventual formation of a pulsion diverticulum.

Dysphagia is a consistent symptom of hypopharyngeal diverticulum. There may be regurgitation of food, choking, aspiration, chronic cough, and occasionally, in advanced cases, esophageal obstruction or disabling aspiration pneumonia. Diagnosis from the clinical features and the contrast esophagogram is straightforward. The only treatment is surgical.

In 1960 Dohlman[3] reported an endoscopic surgical technique for hypopharyngeal diverticulum using an esophagoscope with a double-lipped distal end and electrocautery to divide the muscular septum between the esophagus and the pouch. This technique was widely used until Van Overbeek et al[4] in 1984 introduced microendoscopic surgery for hypopharyngeal diverticulum using the operating microscope and either electrocautery or a carbon dioxide laser to achieve the transmucosal division of the muscular sphincter. Their experience with 274 patients confirmed endoscopic treatment of hypopharyngeal diverticulae as a reliable method using a specially designed esophagoscope and the operating microscope to provide excellent exposure of the tissue bridge between the esophagus and the diverticulum during surgical division. In 1987 Holinger and Benjamin[5] reported a new endoscope (Karl Storz) for endoscopic diverticulotomy — basically a modification of the original Dohlman endoscope and the endoscope of Van Overbeek. Division of the posterior cricopharyngeal muscle fibers at the UES is the essential part of endoscopic surgery, whether performed by electrocautery, the carbon dioxide laser, or the potassium-titanyl-phosphate (KTP/532) laser.[6]

Hypopharyngeal diverticulum is an uncommon disease, mostly of elderly patients who have chronic, slowly progressive dysphagia. Endoscopic diverticulotomy effectively divides the muscular diverticuloesophageal party wall, creating 1 lumen. Although the pouch has not been removed, it no longer fills and food passes into the esophageal lumen, with relief of dysphagia and elimination of aspiration caused by overflow of sac contents into the larynx. The aim is not removal of the diverticulum, but cricopharyngeal myotomy to eliminate food trapping in the pouch.

This paper reports the results of microendoscopic diverticulotomy using the Holinger-Benjamin diverticuloscope and the carbon dioxide laser on 34 patients and introduces a second, slimmer diverticuloscope designed for those few patients in whom anatomic features such as large teeth, limited jaw opening, a stiff cervical spine, or large cervical osteophytes make endoscopic exposure of the hypopharynx and upper esophagus difficult.

METHODS

The records of 34 patients treated by microsurgical

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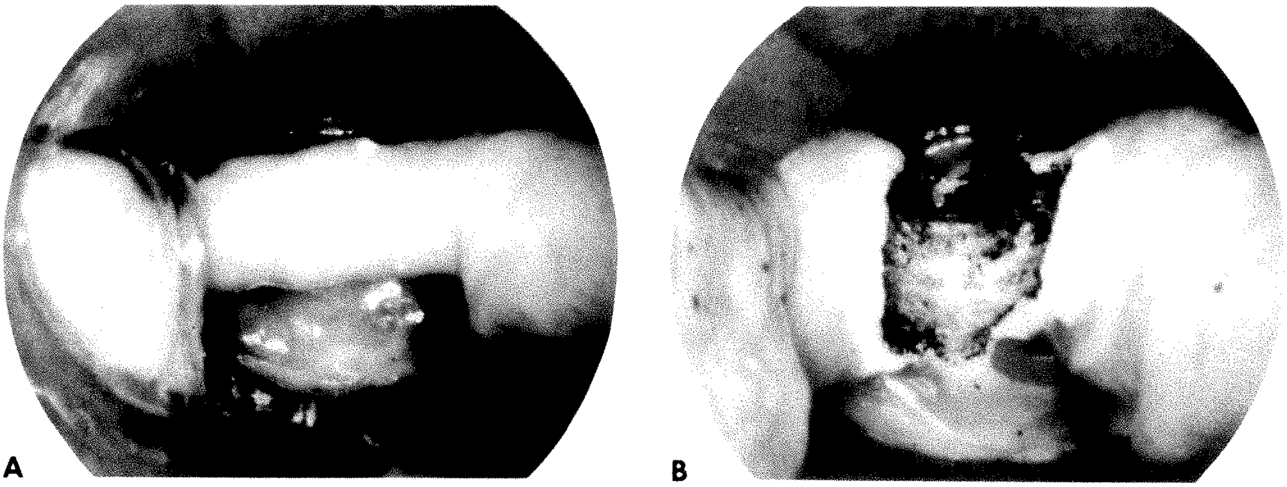

Fig 1. Prominent muscular septum between esophageal lumen and pharyngeal pouch. A) Before commencing laser division. B) Partly divided. Transverse muscle fibers can be seen.

endoscopic carbon dioxide laser diverticulotomy at Royal North Shore Hospital, Sydney, from 1987 through 1992 were reviewed. A diagnostic barium swallow study had confirmed the presence and the size of each hypopharyngeal pouch.

Surgical Technique. The patients were admitted on the morning of surgery, which was performed by one of the authors or by a fellow. Under relaxant general anesthesia using a peroral endotracheal tube 1 or 2 sizes smaller than "average" so as not to hinder endoscopy, the Holinger-Benjamin double-lipped diverticuloscope is introduced into the right pyriform fossa and moved medially to the postcricoid region, allowing the anterior lip of the diverticuloscope to pass into the esophageal lumen and the shorter posterior lip into the lumen of the diverticulum. In this way the muscular septum is prominently displayed between the 2 lips (Fig 1). The diverticuloscope is suspended (Fig 2) with the distal crossbar of the suspension apparatus resting on a Mustard table, which itself is firmly attached to the side of the operating table.[7] If the operating table is raised, lowered, or tilted, the Mustard table, the suspension system, and the diverticuloscope, being a fixed unit, move together without further adjustment.

The pouch is cleaned of any accumulated food or debris and closely inspected with a rigid rod lens telescope to exclude malignancy. The microscope, with a 400-mm lens, is focused on the muscular bar in the center of the field of view, between the lips of the diverticuloscope, and the laser is used at a power setting of 5 to 10 W with a spot size of approximately 1.5 mm. A video camera on the beam-splitter of the microscope allows the anesthesiologist and other operating room personnel to follow the progress of the procedure.

The muscular wall is divided in the midline (Fig 1) for a distance of about 2 cm, depending on the size of the pouch. The muscle fibers can be seen as they retract laterally during division and release of the posterior fibers of the cricopharyngeus muscle, leaving a wedge-shaped wound.

Intravenous fluids are continued for 24 hours, then clear fluids are given by mouth for 24 hours before commencement of food intake. All patients receive antibiotics.

Each patient has an immediate postoperative chest x-ray study, and thereafter regular clinical examination of the neck and auscultation of the chest to detect possible surgical emphysema and pneumomediastinum. In the first part of the series a nasogastric feeding tube was positioned for 24 hours, but in the second part of the series a nasogastric tube was not used.

RESULTS

Of the 34 patients (see Table), 20 were men and 14 women. The ages ranged from 45 to 90 years, with a mean age of 65 years. All patients had chronic, slowly progressive dysphagia.

No patients were considered unfit for the procedure, although 7 were 80 years of age or more, and a number of medical and surgical conditions coexisted (see Table). In the early part of the series the average hospitalization after uncomplicated operations was 5 days, and in the later part of the series, 4 days. There were no major complications, although early in the series 2 patients had a minor leak of air in the neck detected by x-ray study; both were treated conservatively and both made a rapid recovery. Patients were asymptomatic for swallowing within a week; none had prolonged hospitalization; none complained of

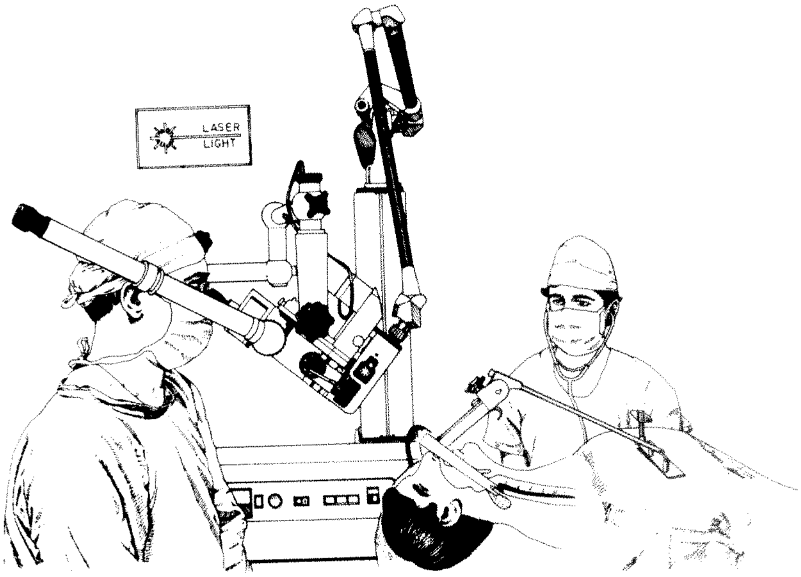

Fig 2. Microscope and carbon dioxide laser in place. Diverticuloscope is suspended, and patient's face will be protected by moist towel.

pain in the postoperative period. One patient had incomplete division of the septum and required a revision operation; otherwise, the results were satisfactory in all cases, which included the 2 patients who had previously had unsuccessful surgical procedures. The diverticuloscope could not be introduced in 2 individuals, hence the design of a new, smaller instrument.

DISCUSSION

The operations currently advocated in the literature include the single-stage transcutaneous diverticulectomy combined with cricopharyngeal myotomy and endoscopic diverticulotomy.[8,9] Dohlman's endoscopic operation using electrocoagulation now appears to have been replaced by endoscopic procedures using the microscope and the laser (either the carbon dioxide or the KTP/532) for a more predictable, controlled, simple operation with excellent visualization and universally good results with few complications.[2,4-7]

Note than Van Overbeek et al[4] compared carbon dioxide laser diverticulotomy with conventional electrocoagulation diverticulotomy and found that both techniques gave good results with no significant comparative difference, but the laser patients suffered less pain during the first days postoperatively and swallowed more readily. Van Overbeek et al regarded use of an operating microscope as a great improvement.

The surgical technique is important. Relaxant general anesthetic is administered with due precautions for coexistent disease such as ischemic heart disease. The Holinger-Benjamin diverticuloscope[5] is an improvement on the original Dohlman endoscope. It has a wider proximal end (35 x 22 mm) for binocular visualization through the microscope, relatively safe use of the laser, and easy introduction of instruments and suction. A smoke evacuator channel is provided on one side, and a fiberoptic light-carrier on the other. There is a lightweight, rigid stainless steel handle for easy insertion and rapid suspension using the Karl Storz adjustable suspension system, thus allowing the surgeon freedom to use both hands, and the foot of this self-retaining diverticuloscope holder rests on a Mustard table, which is firmly fixed to the operating table. Use of the laser requires the usual precautions, and if desired, moist patties can be placed to protect the esophagus and the pouch. Division of the septum is critical: there must be clear exposure, the defocused laser beam is used at 5 to 10 W in the midline, and as the laser creates a small zone of coagulation on each side and seals small blood vessels to that, bleeding is usually absent or minimal, but electrocoagulation of an oozing vessel with an insulated suction tip is occasionally necessary. The operation is essentially a transmucosal myotomy of the cricopharyngeus muscle to join the lumen of the pouch and the esophageal lumen into one to facilitate drainage and prevent accumulation of food.

The cricopharyngeus is divided for about 2 cm, depending on the size of the pouch, with the muscle fibers watched as they retract on each side. Care must be exercised to minimize the risk of perforation, surgical emphysema, and subsequent infection. All patients receive antibiotics, intravenously at first and then orally. A nasogastric tube for postoperative nutrition is optional; we no longer use it routinely.

The total anesthetic and operative time for the laser diverticulotomy is usually 20 to 25 minutes. Patients swallow fluids within 24 hours and soft food within

PATIENTS RECEIVING MICROENDOSCOPIC DIVERTICULOTOMY FOR HYPOPHARYNGEAL DIVERTICULUM

Pt No.	*Age*	*Sex*	*Days in Hospital*	*Consistent Medical Problems*	*Complications*
1	55	F	8	Dohlman diathermy elsewhere with perforation, mediastinitis, and right vocal cord paralysis	
2	90	F	13	Renal disease, previous pulmonary embolus, IHD	Oliguria
3	58	F	9	Multiple sclerosis	
4	45	M	8	Healthy	Air on x-ray study, uneventful recovery
5	47	M	6	Healthy	
6	87	F	8	Asthma	
7	84	F	5	Treated lymphoma, IHD	
8	64	M	8	Right carotid stenosis, IHD, cervical spondylosis	Air on x-ray study, uneventful recovery
9	78	M	7	Hypertension	
10	54	F	7	Healthy	
11	47	M	6	Healthy	
12	55	M	4	Healthy	
13	61	M	4	Duodenal ulcer	
14	81	F	5	Hypertension, hiatal hernia	
15	66	M	4	Gout	
16	80	M	5	IHD, peptic ulcer	
17	71	M	4	IHD	
18	67	M	5	Cervical spondylosis	
19	78	M	4	Healthy	
20	77	F	5	Hypertension	
21	85	F	5	Healthy	
22	89	F	5	Hypertension, hiatal hernia	
23	43	M	4	Healthy	
24	65	M	4	Two previous external operations; symptoms returned after 2 months	Required second operation
25	76	F	5	Hypertension, chronic renal failure, osteoarthritis	
26	68	M	4	Lung carcinoma, chronic airway disease	
27	71	F	4	Healthy	
28	63	M	4	IHD, diabetes	
29	79	M	3	IHD, hypertension, diabetes	
30	74	F	3	Previous laser of pouch by another surgeon	
31	74	M	4	Healthy	
32	76	F	4	Thoracolumbar disc disease	
33	62	M	1	IHD	Unable to pass scope
34	69	M	1	Healthy	Unable to pass scope

IHD — ischemic heart disease.

48 hours.

All patients are informed before operation that if division of the muscle is inadequate and there are significant residual postoperative symptoms, a second procedure might be necessary. A barium swallow study after operation is necessary only if any dysphagia persists. Van Overbeek[2] stated that even those patients in whom there was radiographic evidence of a residual diverticulum were usually free of symptoms.

The senior author (B.B.) has treated pharyngeal pouches surgically for over 25 years: at first by the then treatment of choice, surgical excision of the pouch and myotomy of the cricopharyngeal muscle; then later by the Dohlman diathermy technique; and now, for the last 10 years, by endoscopic treatment with the carbon dioxide laser. Van Overbeek[2] reported on 508 patients treated endoscopically between 1964 and 1988, with the microscope used from 1981, with a very low complication rate. Microendoscopic laser diverticulotomy is a less invasive, relatively simple, quick, precise, and relatively safe procedure requiring short hospitalization and being able to provide complete relief of symptoms. The laser technique is well suited to treatment of the very old or debilitated patient in whom there might be risk of anesthetic, perioperative, or postoperative complications, but need no longer be reserved for older patients.

Endoscopic treatment with the microscope is minimally invasive, relatively safe, and effective and can be considered the treatment of choice for patients of all ages, whether the pouch is large or small.

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4TH INTERNATIONAL ACADEMIC CONFERENCE IMMUNOBIOLOGY IN OTOLOGY, RHINOLOGY AND LARYNGOLOGY

The 4th international academic conference Immunobiology in Otology, Rhinology and Laryngology will be held in Oita, Japan, April 4-7, 1994. For further information contact Goro Mogi, MD, Dept of Otolaryngology, Oita Medical University, Hasama-machi, Oita 879-55, Japan; telephone 81-975-49-4411 ext 2912 or 2913; fax 81-975-49-0762.

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FOURTH RESEARCH WORKSHOP ON THE BIOLOGY, PREVENTION, AND TREATMENT OF HEAD AND NECK CANCER

The Fourth Research Workshop on the Biology, Prevention, and Treatment of Head and Neck Cancer, sponsored by the American Society for Head and Neck Surgery and the Society of Head and Neck Surgeons, will be held in Arlington, Virginia, on September 8-11, 1994. For further information, contact We Plan Meetings, Inc, Ruth C. Enquist, President, 1503 15th St NE, Rochester, MN 55906; telephone (507) 285-1523; fax (507) 281-8328.

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POSTERIOR GLOTTIC FIXATION IN CHILDREN

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Vocal cord fixation from posterior glottic stenosis may produce progressive airway obstruction. Treatment involves scar excision with adjunctive procedures on healthy tissue, including arytenoidopexy, arytenoidectomy, cordectomy, and cordotomy. Twenty-five children with posterior glottic stenosis were studied; 6 had vocal cord fixation in the midline and 6 had limited vocal cord abduction. All were tracheotomy-dependent because of posterior glottic stenosis and secondary impairment of vocal cord mobility. All children were decannulated after scar incision and widening of the laryngeal framework with posterior cricoid split and stenting. Cartilage grafting was used in 11 patients to maintain an adequate glottic lumen. Ten regained full vocal cord mobility. One had limited adduction, while another's cords were refixed in the midline. A second procedure in the latter patient resulted in limited abduction. Aspiration did not occur in any of the patients, and the voice results were good. Scar incision with cricoid split, cartilage grafting, and stenting is an excellent method for treating posterior glottic fixation without destroying healthy tissue.

KEY WORDS — child, glottic stenosis, larynx, vocal cord fixation.

INTRODUCTION

Posterior laryngeal scarring most commonly occurs from prolonged endotracheal intubation. Ulceration of the mucosa from pressure, followed by secondary infection, perichondritis, chondritis, and formation of granulation tissue, leads to scar formation and arytenoid fixation. In children it is the subglottis that is most involved, being the narrowest part of the airway because of the complete ring of the cricoid. Arytenoid fixation can occur from external scarring, band formation between the vocal processes, or actual involvement of the multiaxial, diarthroidal cricoarytenoid joint.

Bogdasarian and Olson[1] classified posterior glottic stenosis into the following types. Type I is a vocal process adhesion. Type II is posterior commissure stenosis. Type III is posterior commissure stenosis with unilateral cricoarytenoid ankylosis, and type IV is posterior commissure stenosis with bilateral cricoarytenoid ankylosis.

Whited[2] classified this condition into 2 types. In type I, the scarring pattern is in the interarytenoid plane and inferiorly along the internal surface of the cricoid lamina. Type II is fibrous banding between the vocal processes. He estimated the incidence in adults to be around 6%. Cohen[3] was the first to describe "pseudolaryngeal paralysis" in 7 children with vocal cord fixation.

The treatment of this relatively rare condition has been by dilation, steroid injection, and endoscopic scar excision, including laser arytenoidectomy. There exist a variety of external surgical approaches through a laryngofissure, including arytenoidectomy and scar excision with mucosal flaps and stenting. Arytenoidectomy and vocal cord lateralization have been reported to be successful in treating airway obstruction from posterior glottic fixation, yet they can weaken the voice and cause aspiration, necessitating further surgical intervention.[4] Arytenoidectomy to treat patients with ankylosis has also been reported to impede the successful lateralization of the vocal cords in case of failure.[5]

Posterior glottic fixation treated by scar incision, posterior cricoidotomy with stenting, and cartilage grafting, when feasible, resulted in an excellent airway outcome (Fig 1) and good voice results. This is a report describing the pathologic findings, surgical technique, and outcome in 12 children.

PATIENTS AND METHODS

Between December 1986 and July 1992, 25 tracheotomy-dependent patients with glottic stenosis from endotracheal intubation were evaluated. All patients underwent open surgical correction, with tracheotomy decannulation in all. For the purpose of this report, children who had total glottic stenosis, concomitant vocal cord paralysis, anterior and posterior glottic stenosis, vocal cord fusion resulting in thick webs, fibrous bands between the vocal processes, or posterior glottic stenosis with significant stenosis elsewhere were excluded. Only patients with arytenoid fixation due to Whited[2] type I or Bogdasarian and Olson[1] type III or IV stenosis were included.

There were 12 patients, 9 boys and 3 girls, ranging

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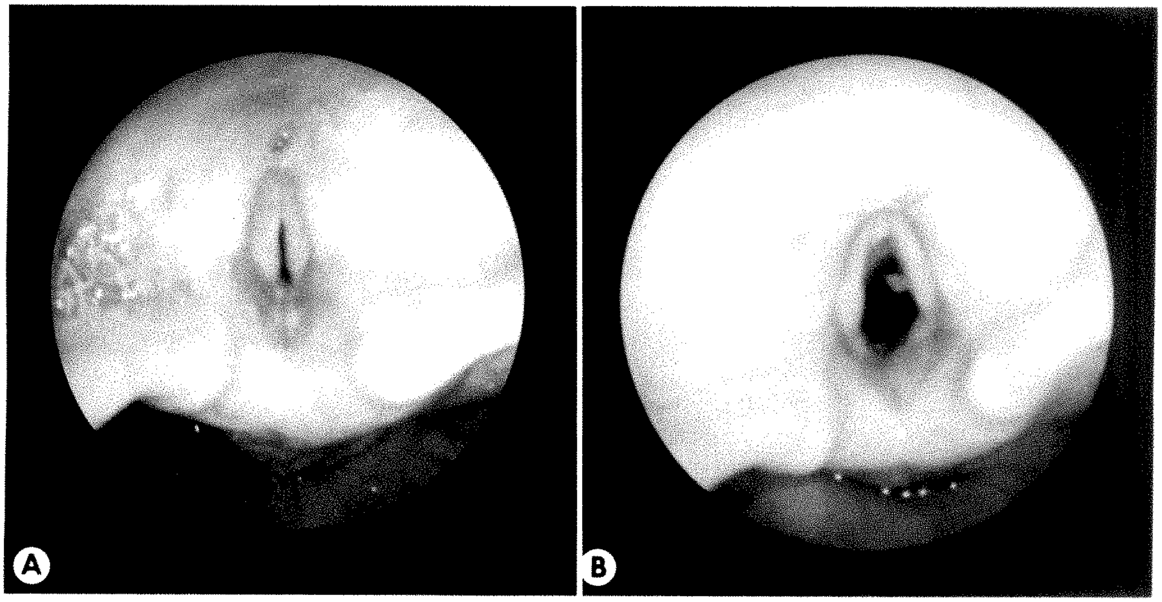

Fig 1. (Patient 4) Endoscopic views of larynx. A) Preoperative assessment showing posterior glottic scar. B) Postoperative assessment. Note improvement in glottic airway and tracheotomy tube in tracheal lumen.

in age from 1 year 5 months to 19 years 7 months. Prior failed treatment included dilation (1 patient), laser scar excision (2 patients), and laryngeal reconstruction (2 patients). Specifically designed data sheets filled at the time of evaluation and treatment were reviewed. Vocal cord mobility was assessed with flexible fiberoptic laryngoscopy with the patient awake and in the sitting position. Vocal cord mobility was listed according to the categories mobile, limited abduction, or fixed. Finally, endoscopic examination in the operating room was performed.

Anesthesia is achieved with ventilation through the tracheotomy tube. The larynx is examined with a rod lens system telescope. Visual assessment of vocal cord mobility is done with the patient under spontaneous breathing and the tracheotomy intermittently plugged. In the presence of posterior glottic scarring, failure of the vocal cords to attempt to move during fiberoptic and rigid endoscopy is an indication for electromyography, to rule out recurrent laryngeal nerve paralysis. The surgical technique of electromyography has been described elsewhere in detail.[6] Sampling of both the thyroarytenoid and posterior cricoarytenoid muscles on each side is performed. The diagnosis of posterior glottic fixation is established if there is no nerve paralysis. Electromyography was essential in confirming posterior glottic fixation in 4 patients.

The larynx and subglottis are exposed, and an anterior cricoid split is performed. If there is anterior subglottic scarring, then the incision is extended inferiorly so that the whole anterior subglottic and upper tracheal scar is incised in the midline. Exposure of the posterior larynx through the anterior subglottic incision, although advisable, can be difficult,[2] and in 10 of the 12 patients an anterior laryngofissure was performed. The posterior glottic scar is incised in the midline, and a posterior vertical cricoidotomy is performed down to the hypopharyngeal mucosa. If the vocal cords' mobility is limited, the interarytenoid muscle is not divided. The tip of the boat-shaped cartilage graft is inserted between the arytenoids.[7] Despite release of the scar, if palpation reveals complete arytenoid fixation with cricoarytenoid joint ankylosis, then the cartilage graft is inserted between the arytenoids to achieve maximum widening of the posterior glottis. An Aboulker stent is placed in the reconstructed site.[8,9] If there is an accompanying anterior subglottic or upper tracheal stenosis, a cartilage graft is inserted.[10]

Voice and speech evaluations were performed. A psychoacoustic evaluation was done by a speech-language pathologist experienced in voice disorders. A voice disorder is defined as vocal production that during communication interaction calls attention to itself, such as hoarseness or breathiness. Aberrant vocal patterns were observed, such as aberrant pitch patterns, frequent duration in particular vocal quality, frequent duration in intensity, aberrant respiratory patterns, and pharyngeal muscular tension. These voice patterns were observed during as many different voice tasks as possible, by means of a standardized voice assessment.

Acoustic analysis was done by recording the voice during psychoacoustic evaluation and analyzing it with Mac Speech Lab II (GW Instrument, Cam-

TABLE 1. ENDOSCOPIC FINDINGS AND RESULTS

Pt No.	*Age*	*Additional Site of Stenosis*	*Right Vocal Cord*		*Left Vocal Cord*		*Duration of Follow-up*
			Preop	*Postop*	*Preop*	*Postop*	
1	1 y 10 mo	Circ SG	Fixed	Mobile	Fixed	Mobile	7 y 4 mo
2	5 y 11 mo	Anterior SG	Limited abduction	Mobile	Limited abduction	Mobile	2 y 9 mo
3	2 y 6 mo	Circ SG	Absent abduction	Mobile	Absent abduction	Mobile	3 y 3 mo
4	19 y 7 mo	Posterior SG	Fixed	Mobile	Fixed	Mobile	5 y 4 mo
5	2 y 4 mo	Circ SG	Limited abduction	Mobile	Limited abduction	Mobile	3 y 7 mo
6	1 y 5 mo	Posterior SG	Limited abduction	Mobile	Limited abduction	Mobile	5 y 1 mo
7	1 y 9 mo	Circ SG	Limited abduction	Mobile	Limited abduction	Mobile	4 y 10 mo
8	13 y 7 mo	Posterior SG	Fixed	Mobile	Fixed	Mobile	3 mo
9	4 y 1 mo	Circ SG	Fixed	Mobile	Fixed	Mobile	4 y 7 mo
10	2 y 3 mo	Circ SG	Limited abduction	Mobile	Limited abduction	Mobile	1 y
11	12 y 11 mo	Posterior supraglottic, tracheal	Fixed	Limited adduction	Fixed	Limited adduction	1 y 6 mo
12	9 y 4 mo	None	Fixed	Mobile for 3 y	Fixed	Mobile for 3 y	3 y
	12 y 4 mo	None	Fixed	Limited abduction	Fixed	Limited abduction	1 y 3 mo

Patient 12 had 2 procedures.
Circ — circumferential, SG — subglottic.

bridge, Mass) and Visi-pitch (Kay Elemetrics, Pine Brook, NJ).

RESULTS

Endoscopic evaluation did not show any bulky arytenoids or congenital interarytenoid webs.[11] All patients had posterior glottic stenosis. Other sites of stenosis are listed in Table 1.

Vocal cord fixation in the midline was present in 6 patients, and limited abduction in another 6. Symmetric involvement of the vocal cords was present in all 12 patients. The duration of stenting in 11 patients who had posterior grafts ranged from 4 to 9 weeks, and decannulation was achieved at an average of 7 (range 2 to 20) weeks after removal of the stents. In 1 patient (patient 9), the absence of rigid cricoid cartilage precluded the use of a graft, and stenting for 10 months was therefore necessary. Endoscopy was performed for assessment of the airway and removal of granulation tissue. The number of endoscopies per patient ranged from 3 to 7, with an average of 4.

All patients have been decannulated, with a follow-up period between 3 months and 7 years 4 months (Table 1). Normal vocal cord mobility returned in 10 patients. One patient (patient 11) has limited adduction, while another patient (patient 12) needed a second procedure when the vocal cords partially refixed 3 years after the initial surgery. He is decannulated, but has limited vocal cord mobility.

Aspiration or feeding difficulties were not encountered in any of the patients.

Psychoacoustic and acoustic analysis evaluations are shown in Table 2. Postoperative evaluations were done 6 months after decannulation whenever possible. Adequate evaluations could not be performed on 3 patients because of out-of-state residence, very young age, the presence of tracheotomy, or severe laryngeal disorders causing aphonia. All children have a postoperative functional voice. Voice disorders present preoperatively persisted postoperatively. Preoperative respiratory and pharyngeal tension was present in 8 of the 9 evaluated children. It disappeared only in 2 postoperatively.

The acoustic analysis results show a trend of improvement in fundamental frequency (F0) without any significant deterioration in frequency range (Table 2). Preoperative and postoperative values are available on 6 patients. Only postoperative values could be obtained on 2 patients. The F0 improved postoperatively in 3 children, deteriorated mildly in 1, and barely changed in 2. The postoperative frequency range widened in 3, narrowed in 2, and changed minimally in 1. Jitter values were abnormal in all patients. Jitter decreased postoperatively in 3, increased in 1, and changed minimally in 2.

DISCUSSION

Posterior glottic fixation is a distinct entity that can easily be confused with vocal cord paralysis or a congenital interarytenoid web. Microdissection and laser division have not been successful in treating congenital interarytenoid web, and decannulation

TABLE 2. VOICE EVALUATION

Pt No.	*Normal F0 for Sex and Age (Hz)*	*Time of Evaluation*	*Frequency (Hz)*			*Jitter (%)*	*Functional Voice*	*Voice Disorder*	*Respiratory and Pharyngeal Tension*
			Max	*Min*	*F0*				
1	370-525	Postop	386.8	57.2	152.7	25.7	Yes	Yes	Yes
2	300-390	Preop	678.0	109.1	252.2	10.22	Yes	Yes	Yes
		Postop	269.2	208.6	244.8	12.82	Yes	Yes	Yes
3	340-460	Preop	305.3	148	181.4	11.42	ND	ND	Yes
		Postop	647.2	57.2	281.9	20.58	Yes	Yes	No
4	175-245	Preop					Yes	Yes	No
		Postop					Yes	Yes	No
5	340-460	Preop	284.3	54.5	103.7	24	Yes	Yes	Yes
		Postop	274.3	66.9	212.5	7.64	Yes	Yes	Yes
8	155-220	Preop	551	49.1	187.8	19.88	Yes	Yes	Yes
		Postop	261.4	63.7	134	21.65	Yes	Yes	Yes
10	370-525	Preop	198.6	61.9	175	11.37	No	Yes	Yes
		Postop	364.4	84.8	288.8	7.2	Yes	Yes	Yes
11	155-230	Preop					Yes	Yes	Yes
		Postop	301.7	66.6	221.1	18.12	Yes	Yes	No
12	170-245	Preop	186.4	105.4	139.9	9.4	Yes	Yes	Yes
		Postop	224.5	94.1	134.9	5.9	Yes	Yes	Yes

F0 — fundamental frequency, ND — not determined.

after tracheotomy is usually achieved after several years.[11]

The treatment of posterior glottic fixation should not be confused with the treatment of vocal cord paralysis, since achieving a patent glottic airway will not impede the sphincteric closure at the glottic or supraglottic level. Aspiration should be of little concern if there is no vocal cord paralysis.

The treatment of vocal cord paralysis in children, despite clinical manifestations similar to those of posterior glottic fixation, requires a different approach. A wait-and-see policy is advocated, since a large number of these children improve spontaneously.[12] Treatment is with endoscopic or open surgical techniques aimed at arytenoidectomy; arytenoidopexy with lateralization of the vocal cords; and possibly reinnervation. Posterior cordectomy with carbon dioxide laser in adults has been reported to achieve decannulation and satisfactory voice results.

Cricoarytenoid joint ankylosis in adults has been described following rheumatic disease, gout, tuberculosis, and syphilis. Arthritis is rare in children.[13] Cricoarytenoid joint ankylosis from long-term vocal cord paralysis has been described in animal models; however, it is not clinically significant in humans.[14] It is unlikely that children with an initial diagnosis of recurrent laryngeal nerve paralysis who recover will continue to have vocal cord fixation because of cricoarytenoid joint fixation.

The traditional surgical repair of posterior glottic fixation focuses on scar excision and resurfacing, mainly in older patients. The treatment in children[3,15-17] seems to be less successful than in adults.[1,2,5,18,19] Laser surgery, either by division or microtrapdoor flap,[20,21] is occasionally successful, depending on the severity of the scarring. The key factor is the presence of a posterior commissure, mucosally lined sinus, or fistula posterior to the scar that is fixing the vocal processes. Laser arytenoidectomy with cricopharyngeal myotomy has been reported to be successful in adults with severe stenosis.[22]

In more severe scarring, the use of a laryngofissure, scar excision, and a mucosal advancement flap from the interarytenoid or aryepiglottic fold is recommended.[23,24]

Prior laser treatment in 2 patients failed and led to serious complications and possible progression of disease. One patient (patient 8) presented with severe posterior glottic stenosis and bilateral vocal cord fixation after a fire resulting from an attempt to treat the posterior glottic stenosis with a carbon dioxide laser. Another child (patient 11) was referred with recent onset of dyspnea despite the presence of a patent tracheotomy. Eleven laser procedures to repair the posterior laryngeal stenosis had failed. Endoscopy revealed posterior glottic and supraglottic stenosis (Fig 2) and severe lower tracheal stenosis that necessitated emergency repair under partial cardiopulmonary bypass. There was bony hard, extensive scarring fixing the cricoarytenoid joints. The cartilage graft was inserted between the arytenoids, and decannulation was achieved 4 weeks after removal of the stent, which was kept in place for 4 weeks. The

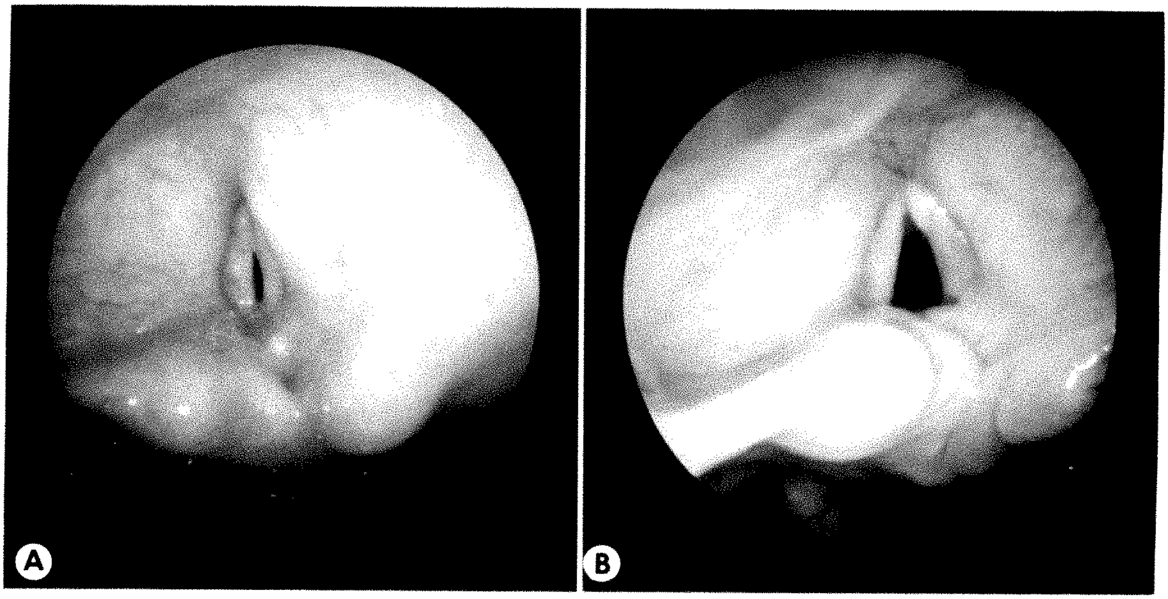

Fig 2. (Patient 11) Endoscopic views of larynx. A) Preoperative assessment showing posterior glottic and supraglottic scarring. This patient had cricoarytenoid joint ankylosis. B) Postoperative view of larynx after insertion of cartilage graft between arytenoids.

child does not aspirate and has an excellent airway. His voice, however, is breathy because of incomplete adduction of the vocal cords.

Bogdasarian and Olson[1] recommended a graded surgical approach for treating posterior commissure scarring, on the basis of their results in 10 adults. In mild cases they performed scar excision, resurfacing with mucosa or split thickness skin graft, and stenting. Arytenoidectomy and hyoid interposition anteriorly were used if there was joint fixation. With the exception of 1 patient with bilateral cricoarytenoid ankylosis, all of their patients were decannulated. The voice was normal in mild stenosis, and hoarse in the more advanced cases of stenosis. Aspiration occurred in 2 of 4 patients who underwent arytenoidectomy. Bogdasarian and Olson indicated that following arytenoidectomy, the innervated vocal cord tends to heal in a position of adduction when compared to the denervated vocal cord. Therefore, bilateral arytenoidectomy in the innervated larynx may fail to establish an adequate airway, necessitating further lumen augmentation.

Whited[2] recommended scar excision to allow unimpeded arytenoid movement and primary closure or a sliding mucosal flap.

Goodwin et al[18] avoided arytenoidectomy and vocal cord lateralization, because they consistently weaken the voice and may cause aspiration. Scar tissue excision and stenting without posterior cricoidotomy were used to treat 6 patients. In 4 patients they used soft stenting for 5 to 7 weeks. Firmer, rolled Silastic stents were used for 6 weeks in 2 larynges. Vocal cord motion improved in all 6 patients, with mobility returning to normal in 3 patients.

Grahne et al[25] reported airway improvement in 13 adults with laryngeal paralysis and stenosis. They divided the scarred interarytenoid muscle and posterior cricoid cartilage vertically down to the esophageal muscles. An Aboulker stent was fashioned and left in position for 4 months. In the present group of patients who underwent posterior cricoidotomy and cartilage grafting, successful results were achieved with a shorter duration of stenting (4 to 9 weeks).

The treatment of posterior laryngeal stenosis in children with fixation of the arytenoids remains a significant surgical challenge.[26] It is essential that arytenoidectomy be avoided in children with posterior glottic stenosis. This is because of the possibility of aspiration, the expected deterioration in voice, and the difficulty of achieving a good airway in possible future repair.

The present technique aims at widening the laryngeal framework and offers the following advantages. Scar incision without excision keeps the denuded laryngeal surface to a minimum. Stenting the anteriorly and posteriorly split cricoid widens the rigid cartilaginous laryngeal framework. Insertion of a cartilage graft posteriorly serves to keep the arytenoids apart and reduces scar tissue buildup. It also reduces the duration of stenting. When grafting is not possible, stenting for a long period is necessary (10 months in patient 9). The use of cartilage grafts leads to early decannulation (average of 7 weeks after stent removal) after short-term stenting (usually 4 to 6 weeks).

The clinical and experimental success of autogenous cartilage grafts in the posterior cricoid has been adequately documented.[27,28] Biopsies performed 3 years after grafting (patient 12) showed viable fibrocartilage.

Cotton[27] reported only 13 (21%) of 61 children undergoing posterior cricoidotomy and cartilage grafting to have normal bilateral cord motion. Twelve had bilateral fixation of the cords or their remnants. The fixation was due to posterior glottic stenosis, fixation of the cricoarytenoid joint, paralysis of the cords, or massive intralaryngeal and submucosal scarring. In some of the cases, there were no recognizable vocal cords. Postoperative assessment of vocal cord movement 6 months after decannulation could not be done because of out-of-state residence. Voice or cry quality was assessed subjectively by the parents or legal guardian. The voice improved in 35, stayed the same in 23, and deteriorated in 3. No subgroup of posterior glottic fixation was highlighted. The author[28] found that the voice quality in 41 children who underwent anterior and posterior cartilage grafting was satisfactory.

With the exception of 1 patient (patient 11) with fused cricoarytenoid joints, arytenoid mobility returned after scar incision. None of the patients underwent lysis of adhesions within the cricoarytenoid joint, and therefore, speech therapy was not recommended. Schaefer et al[29] described vocal cord mobility enhanced by voice therapy after lysis of the adhesions within or adjacent to the cricoarytenoid joint.

Children offer a specific challenge during acoustic analysis, with measurements not achieved in children who are under 3 years of age. Psychoacoustic evaluation is difficult to quantify; therefore, comparing the results among different researchers is impossible. Comparison can only be made to the preoperative voice and established norms. The patients were examined by 1 person, and the validity of results was determined by interjudge reliability. Abnormal pharyngeal and respiratory patterns may disappear after decannulation. All children developed vocal communication postoperatively. The psychoacoustic impressions showed that preoperative voice disorders continue to persist after reconstruction. Glottic gap and tissue stiffness cause breathiness and hoarseness from irregular vibration of the true and false vocal cords. This can be a consequence of long-term endotracheal intubation, repeated dilation, laser scar excision, stenting, or expansion reconstructive surgery.[30] Cricothyroid membrane scarring influences vocal cord tensing and adds to change in voice frequencies.

It is impossible to compare this group of patients to a control group who were treated with other modalities (laser arytenoidectomy, etc). However, in addition to the excellent airway results, the voice evaluation, including acoustic analysis data (Table 2) available on this series of children, objectively shows no deleterious voice effects of the proposed surgical technique. Actually, the vocal quality improved in some children.

CONCLUSION

Posterior glottic fixation in children is not uncommon and must be differentiated from vocal cord paralysis. Procedures aimed at increasing the airway lumen by tissue excision have not been uniformly successful. Chronic aspiration and poor voice results have been reported.

Return of vocal cord mobility, tracheotomy decannulation without aspiration, and good voice can be achieved by widening the laryngeal framework. Scar incision without excision reduces the denuded laryngeal surface. The laryngeal framework is widened by anterior and posterior cricoid split and by stenting. Posterior cartilage grafting reduces scar tissue buildup and the duration of stenting.

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ASSOCIATION FOR RESEARCH IN OTOLARYNGOLOGY

The 1994 Midwinter Meeting of the Association for Research in Otolaryngology will be held in St Petersburg Beach, Florida, February 6-10, 1994. For information, contact Michele Johnson, Executive Secretary, 431 E Locust St, Suite 202, Des Moines, IA 50309; telephone (515) 243-1558; fax (515) 243-2049.

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NEW TECHNIQUE FOR THE STERILE INTRODUCTION OF FLEXIBLE NASOPHARYNGOLARYNGOSCOPES

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ELKINS PARK, PENNSYLVANIA

Since the inception of flexible fiberoptic endoscopes, disinfection of these instruments has been a problem. Soaking in glutaraldehyde does not always achieve sterilization, and often damages the scopes. Ethylene oxide can sterilize endoscopes; however, it is economically impractical because of a required downtime of 24 hours. Thus, it is obvious, especially with respect to human immunodeficiency virus, hepatitis B virus, and *Mycobacterium*, that a new technique to attain sterility is necessary. This paper discusses a new method of sterile introduction of the flexible nasopharyngolaryngoscope. The technique employs disposable sterile sheaths that are prepackaged and made from a thermoplastic elastomer with a clear optical end. The sheaths can be applied in seconds and tightly adhere to the flexible insertion portion of the scope. Results to date indicate that the performance of the endoscope is unhindered by using the sheaths. Furthermore, there has been no break in the integrity of the sheaths or damage to instruments. It is our opinion that these devices will greatly improve the level of sterility while at the same time reducing costs and downtime.

KEY WORDS — endoscope, flexible scope, nasopharyngolaryngoscope, sterile sheath.

In the past, when a mirror was used to examine the nasopharynx and larynx, sterilization was achieved by merely immersing the instrument in boiling water. With the advent of flexible endoscopes, sterilization became more difficult.[1] Although there have been many reports of patient cross-contamination with other flexible endoscopes, none have been published involving the nasopharyngolaryngoscope since its introduction in 1976.[2] However, we cannot be complacent because of the lack of reported contamination in otolaryngology. It is clear that a secure and effective method of sterile introduction of the flexible nasopharyngolaryngoscope is necessary to ensure our patients' safety and peace of mind. The recently introduced sterile endosheath from Vision Sciences of Natick, Massachusetts, may provide the solution.

At present, there are generally 2 methods used to attain sterilization of the flexible nasopharyngolaryngoscope. The most common procedure is to wash and soak the instrument immediately after use in order to prevent secretions from drying on the scope. The scope is placed under tap water, scrubbed carefully with soap and water, rinsed in isopropyl alcohol, and finally soaked in glutaraldehyde.

Despite the fact that this method has become standard procedure, there are major drawbacks. This process takes about 30 minutes to complete — a rather long period of downtime in a busy medical practice. A recent communication indicates that glutaraldehyde is irritating, toxic, and sensitizing.[3] Furthermore, the prolonged use of glutaraldehyde can have a damaging effect on the scope itself, deteriorating the coating that surrounds the control portion of the instrument. Under the microscope, small cracks and crevices are evident. These are host areas in which bacteria and viruses may be entrapped and reproduce. The cost to repair a worn nasopharyngolaryngoscope is very high, not including the inconvenience of temporarily losing the scope's availability.

Another frequently used method of sterilization of endoscopes employs ethylene oxide. As with glutaraldehyde, the instrument is washed immediately after use. Since the equipment cost of gas sterilization is prohibitive, the gassing procedure is usually completed at a hospital. The sterilization process requires the nasopharyngolaryngoscope to be out of service for 24 hours. This is the major drawback to the technique. Very few practitioners have a sufficient number of nasopharyngolaryngoscopes to allow for their removal from service.

Fear of cross-contamination with all forms of pathogens, including hepatitis B virus, human immunodeficiency virus, and *Mycobacterium tuberculosis*, requires a change in our sterilization technique.[4,5] Recent pronouncements from the Occupational Safety and Health Administration concerning the protection of health care workers from exposure to glutaraldehyde and blood-borne diseases have also forced us to seek better methods of sterilization. Last, economic factors have become a major influence on

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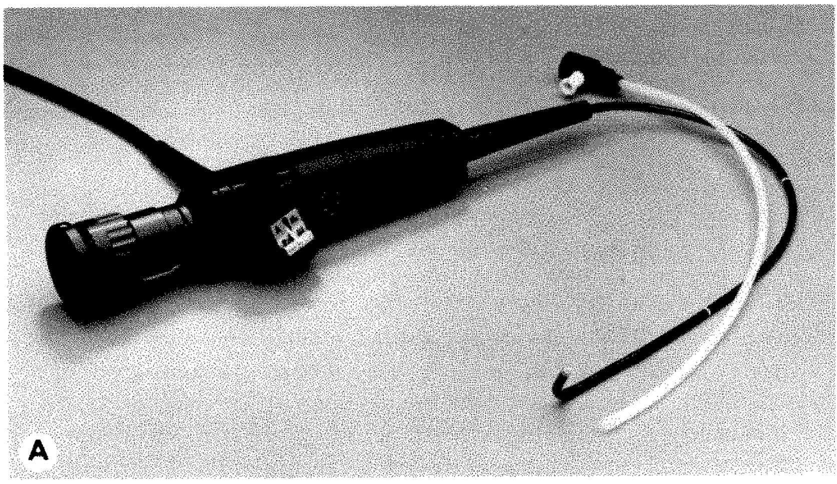

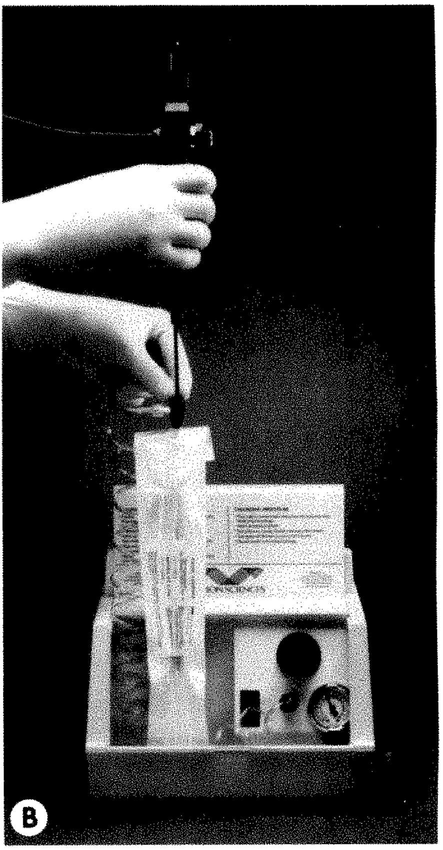

New system for sterile introduction of flexible nasopharyngolaryngoscope employs prepackaged, presterilized, disposable endosheath that eliminates need for soaking or gas sterilization of endoscope. A) Endosheaths are made of soft, colorless, thermoplastic elastomer with clear optical end that fits tightly over nasopharyngolaryngoscope. There is no appreciable change in scope performance. B) Small, quiet air pump is supplied with sheaths. Pump expands sheath slightly so that one can insert nasopharyngolaryngoscope. Endosheaths are supplied in sterile sealed envelopes. Pump is designed with special clip to hold packaged endosheath in place.

how we practice medicine. Medical practice requires cleaning methods that permit minimum downtime, have a reasonable cost, and assure sterilization.

The new system by Vision Sciences for the sterile introduction of flexible nasopharyngolaryngoscopes fulfills most, if not all, of our requirements. It consists of a prepackaged, presterilized, disposable endosheath fabricated to cover the insertion tube of the flexible nasopharyngolaryngoscope. The endosheaths are made from a colorless thermoplastic elastomer with a clear optical end (see Figure, A). The soft, tubular, rubberlike material fits tightly over the nasopharyngolaryngoscope. The sheaths are designed for one-time use. When the sheaths are applied and handled properly by office or hospital personnel, there is a marked reduction in their risk of accidental exposure to all contaminants. With the sheath in place, the nasopharyngolaryngoscope never comes in contact with the patient's secretions.

The actual application of the endosheath is quite easy. A small, quiet air pump is supplied with the sheath. The pump slightly expands the sheath, allowing the nasopharyngolaryngoscope to be easily slid inside. The pump is designed with a special clip to hold a sealed envelope in which there is a plastic tube containing the endosheath (see Figure, B). The envelope is opened by peeling back the upper end, allowing an air tube from the pump to be inserted into a valve on the side of the endosheath. With pressure applied, the scope is then slid into position, with the end of the instrument against the optically clear end of the sheath. Once the sheath is in place, the air pressure is released, and the sheath tightens around the scope. To remove the scope from the sheath, the procedure is repeated and the instrument withdrawn. The entire endosheath is then discarded. The sheaths will be designed to conform to specific nasopharyngolaryngoscopes.

Our initial evaluation began in the spring of 1992 with 42 prototype sheaths and continued until our supply of endosheaths was expended. A 3.3-mm flexible nasopharyngolaryngoscope was used in our study. Its normal diameter was expanded to 3.8 mm with the endosheath in place. We were concerned that the sheath-covered scope would be difficult to slide through the nose because of its "tacky" feel and increased thickness. Yet, when the sheath was wet with water, it became quite slippery and passed more easily than an unsheathed, dry scope. Fogging of the optical tip can be avoided by simply touching the lens to the nasal mucosa.

There was no appreciable change in scope performance. We were pleasantly surprised by our patients' response to the new device. No patient expressed any increased discomfort as compared to examination with an unsheathed instrument. A few, in fact, believed the moistened, sheath-covered scope to be more comfortable.

The only problem encountered with our first series of endosheaths was that a few had an improper-size sealing ring placed in the open insertion end. This problem has been corrected by the manufacturer. The remainder of the endosheaths worked flawlessly. All used endosheaths were returned to the manufacturer and tested for breaks in integrity. None were found.

Downtime between patients with the flexible nasopharyngolaryngoscope prior to use of the sheaths was approximately 30 minutes, including washing and a 20-minute soak in glutaraldehyde. With the endosheath, the entire process has been reduced to less than 1 minute.

We have recently begun using production-model endosheaths and have not encountered any problems. Our nursing personnel have expressed great enthusiasm with the ease of application and are especially grateful at being able to handle contaminated material in a safer and more efficacious manner. Patient acceptance has been excellent, with obvious expressions of relief over the knowledge that they are no longer in danger of cross-contamination. The latter fact is important, because patients fear contraction of acquired immunodeficiency syndrome from nonsterile instruments when being examined. We hope that this means of prevention of cross-contamination of flexible endoscopes will become a universally accepted procedure, as it will reduce morbidity and save lives.

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INDICATIONS FOR OPEN SURGICAL REMOVAL OF AIRWAY FOREIGN BODIES

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Airway foreign bodies can usually be extracted by skillful application of endoscopic techniques. We report our experience in the management of 2 infants in whom sharp, pointed objects dictated consideration for an open surgical approach. Clinical presentation and treatment options will be discussed in the successful management of these 2 patients, one with a crab claw in the subglottis and the other with an electronic diode in the lung. Extensive training and a full complement of modern instruments are required, but in highly selected cases, an open surgical procedure entails less risk than endoscopic extraction.

KEY WORDS — bronchoscopy, bronchotomy, endoscopy, foreign body, thoracotomy.

INTRODUCTION

The techniques for endoscopic management of tracheobronchial foreign bodies were pioneered by Chevalier Jackson over 75 years ago,[1-4] and were so successful that nearly all foreign body removals began to be endoscopic. In a speech before the American Broncho-Esophagological Association in 1921, Jackson stated that there were no indications for open surgical removal of airway foreign bodies.[4]

Today, however, with modern techniques of anesthesia and the relative safety of transthoracic bronchotomy, this absolute position must be modified. Recently, we managed a patient with thoracotomy and bronchotomy in whom endoscopic removal posed enormous technical difficulties and risk.

The purpose of this communication is to report 2 cases of open surgical removal of airway foreign bodies, to review the literature, and to summarize the indications for surgical removal of airway foreign bodies.

MATERIALS AND METHODS

The English-language literature was searched by Medline and cross-referencing to yield 50 reports with interpretable data describing patients with airway foreign bodies.[5-54] The case reports were pooled to provide the data for this paper.

The foreign body experience of the Johns Hopkins Hospital was reviewed for the 30-year period from 1960 to 1990. For this time period, we were able to identify 2 patients out of approximately 300 foreign body cases in whom open surgical techniques were used to remove airway foreign bodies. These cases are described below.

CASE REPORTS

Case 1. An 8-month-old girl was brought to the emergency room after choking on a grape. The patient was initially cyanotic, but after a sharp blow to the back by the mother, the child coughed out a partially chewed grape and a piece of styrofoam. On arrival to the emergency room, the patient was found to have mild stridor. A neck radiograph revealed a subglottic foreign body.

The patient was taken to the operating room, where under mask halothane anesthesia, laryngoscopy and tracheoscopy were performed. A crab claw (Fig 1) was visualized through the glottis, and was easily grasped. However, because of the multiple pointed barbs directed superiorly against the subglottis, traction could only have embedded the object into the undersurface of the glottis. An attempt at rotation failed because of the length of the claw and its multiple points.

The patient was intubated with a small endotracheal tube, and a tracheostomy was performed. The claw was then manipulated endoscopically to the stoma and removed atraumatically. The patient subsequently recovered uneventfully, and she was decannulated 2 days later.

Case 2. An 8-month-old boy was brought to the emergency room with a 2-day history of cough and

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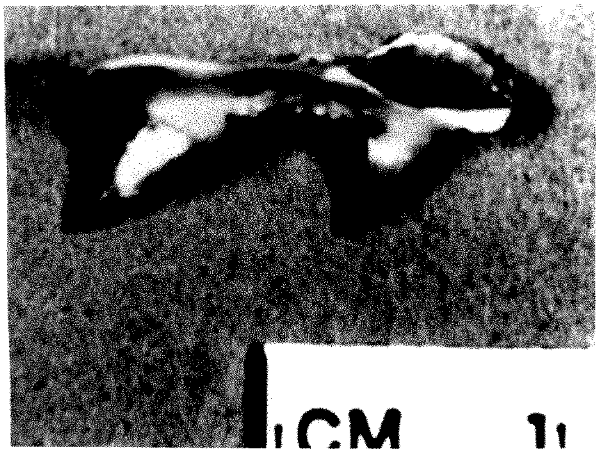

Fig 1. (Case 1) Crab claw removed from subglottis.

fever. The patient was found to be mildly tachypneic, with a temperature of 40°C. The chest radiograph (Fig 2A) revealed a radiopaque foreign body in the left main bronchus. The foreign body was thought to be an electronic diode. The father was a television repairman, but he was unable to produce an exact duplicate.

The patient was taken to the operating room, where under halothane anesthesia, rigid bronchoscopy was performed with a ventilating bronchoscope. The foreign body was visualized with a Hopkins rod telescope in the proximal left main bronchus. One prong was overlying the carina and the other prong was embedded in the lateral wall of the trachea. The medial prong was grasped with a side-curved forceps and gentle traction was applied, but no movement occurred. Attempts to disimpact the foreign body resulted in its displacement into the left lower lobe bronchus.

The patient was then taken to the pediatric intensive care unit and the senior staff was consulted. After 2 days of intravenous antibiotics and steroids, the patient was returned to the operating room for repeat bronchoscopy. The left main bronchus was nearly swollen shut with edema. The foreign body was observed with difficulty in the left lower lobe bronchus, with 1 prong embedded in the superior segment and the other in the left upper lobe bronchus.

Because of the technical difficulty presented by this foreign body in a very small bronchus and the high risk of bronchial perforation, we abandoned the endoscopic approach in favor of proceeding directly with a limited left thoracotomy and bronchotomy. The foreign body (Fig 2B) was then removed and the bronchotomy repaired. The patient recovered without further incident and was discharged from the hospital 10 days postoperatively.

LITERATURE REVIEW

A review of 50 papers yielded 6,693 cases of airway foreign body.[5-54] Not all papers reported on each subject of analysis. Of those reporting complete data, 161 of 6,393 patients (2.5%) required thoracotomy and 104 of 5,296 (2.0%) required tracheostomy. Of the tracheostomies, 52 were performed for laryngeal edema following bronchoscopy, 11 were performed to assist ventilation, 12 were performed as a conduit to introduce the bronchoscope, and only 10 (0.19%) were performed to assist in removing large or obstructing tracheal foreign bodies. The purpose of tracheostomy was not stated in 19 cases.

Of the 161 patients with thoracotomy, 102 underwent bronchotomy and 59 pulmonary resection. There were 2 deaths reported with thoracotomy for airway foreign body (1.2%). From 5,622 patients undergoing endoscopic removal of foreign bodies with mortality data, there were 33 deaths (0.6%). The cause of death was stated as overwhelming infection in 8, hypoxia from obstruction in 8, cardiac arrest in 6,

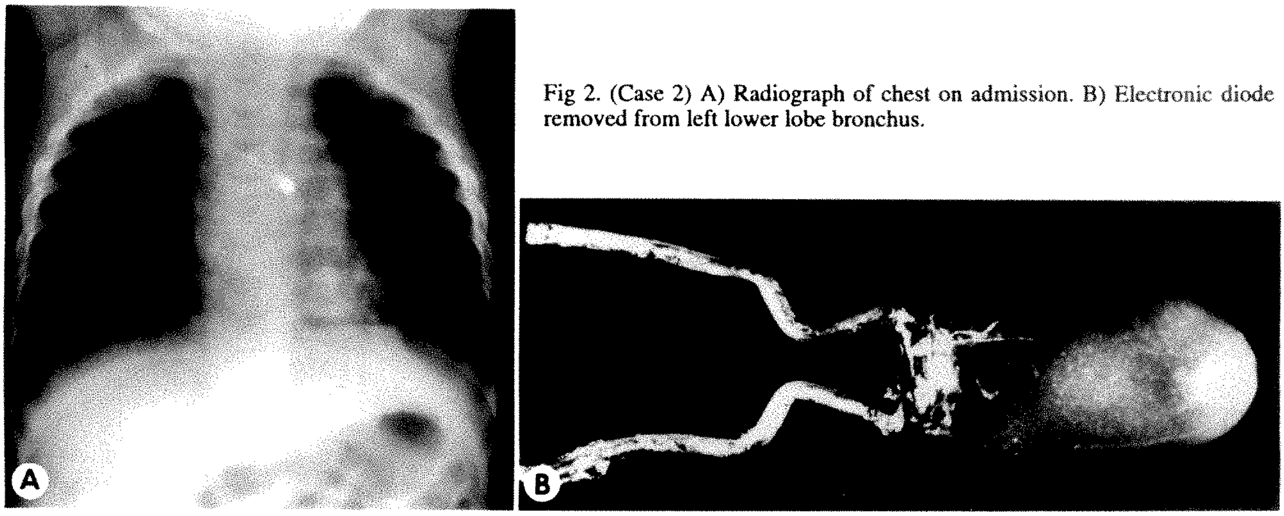

Fig 2. (Case 2) A) Radiograph of chest on admission. B) Electronic diode removed from left lower lobe bronchus.

TABLE 1. FOREIGN BODIES REQUIRING PULMONARY RESECTION

Foreign Body	*No.*
Grass head	13
Vegetable	5
Metal ring	5
Peanut	3
Screw	2
Tack	2
Bone	2
Tooth	1
Seed	1
Miscellaneous	3

TABLE 2. FOREIGN BODIES REMOVED BY BRONCHOTOMY

Foreign Body	*No.*
Pin	9
Tooth	7
Nail	6
Screw	5
Needle	4
Plastic object	4
Double-pointed object	3
Glass object	3
Bead	2
Bone	2
Safety pin	2
Bullet cartridge	2
Peanut	2
Miscellaneous	6

respiratory failure in 3, hemorrhage in 1, and irreversible bronchospasm in 1. In 6 cases the cause of death was not stated.

Pulmonary resection was required for bronchiectasis or chronic infection and abscess. In only 37 of such cases was the type of foreign body identified (Table 1). The most common of these were grass heads, miscellaneous vegetable matter, and metal fragments. Bronchotomy was performed for a number of different types of foreign bodies (Table 2). The most common of these that were identified were pins, teeth, and nails.

DISCUSSION

We present 2 cases requiring surgical intervention for airway foreign body removal. The first required tracheostomy to avoid laceration and potentially permanent injury to the vocal cords and subglottis. The object was too large for all of the razor-sharp points to be sheathed simultaneously, and too large to rotate. A tracheostomy permitted us to extract the foreign body safely with points trailing. Other indications for this technique include acute airway obstruction from a subglottic foreign body or a foreign body too large to be removed through the glottis without risking dislodgment and sudden distal obstruction. A total of only 10 reports of such cases suggests this is a rare occurrence.

The second case was more difficult in that initial failure of endoscopic technique resulted in distal displacement of the foreign body, associated with a high risk of serious complications with endoscopic removal. The object consisted of 2 rather stiff metal prongs diverging from a smooth ceramic body. It could not be bent, and the prongs were too widely spaced to be sheathed simultaneously. Proximal traction resulted only in further embedding of 1 of the prongs in the bronchial wall, and manipulation resulted in distal displacement. Although perhaps the foreign body would not have been impossible to remove, the risk of endoscopic retrieval in a very small bronchus of an object with 2 diverging points exceeded the risk of thoracotomy. Had this case been referred initially to the most experienced endoscopist, conceivably it could have been safely removed endoscopically, but it is unwise to attempt heroic measures when an open approach carries less risk.

A literature review of thoracotomy for airway foreign bodies reveals a low mortality rate. This may be biased by reporting of the best results, but it can reasonably be assumed that the risk in this patient population is acceptably low.

Indications for pulmonary resection seem to be quite standard throughout the literature, with the typical patient having a long-standing foreign body with irreversible changes in the distal lung parenchyma. Interestingly, the most common objects requiring resection were grass heads. These difficult foreign bodies tend to ratchet deeply into the bronchial tree and tenaciously grasp the adjacent mucosa. Successful extraction has been reported by Jackson,[1] but once the lung is destroyed, pulmonary resection is required.

Bronchotomy was performed for a variety of foreign bodies. The most common were pins, nails, and screws. These tend to migrate toward the periphery and are easily displaced distally by inept endoscopic manipulation. When they reach the periphery of the lung, even the most experienced endoscopist may be unable to effect safe extraction.

Teeth can be dangerous foreign bodies, since some may be sharp and difficult to grasp. When tightly wedged distally, they may constitute a scenario for disaster. An intraoperative death occurred in a local community hospital during endoscopic removal of a tooth. Laceration of the tracheal wall resulted in massive hemorrhage (local physician, personal communication, 1991).

Double-pointed objects are notoriously difficult airway foreign bodies. The options for endoscopic removal include 1) bending the object to sheathe both points with the bronchoscope, 2) rotation with the points trailing, and 3) using staple forceps to cover both points. It should be recognized, however, that these foreign bodies may be difficult to manage even for an experienced endoscopist. A bronchotomy may be a safer alternative, especially in small children.

Unfortunately, some foreign bodies are removed by bronchotomy simply because of inadequate training and experience. Before resorting to bronchotomy, referral to a center with an experienced endoscopy staff should be considered.

CONCLUSIONS

Even in the hands of an experienced endoscopist, there are times when an endoscopic approach to airway foreign bodies should be abandoned in favor of an open surgical procedure. These include 1) large objects in the subglottis or trachea that may be better removed by tracheostomy, 2) grass heads resulting in irreversible lung damage and requiring pulmonary resection, 3) foreign bodies embedded in the lung periphery, 4) double-pointed objects impacted within the tracheobronchial tree of small children, and 5) any foreign body for which the risk of endoscopic removal may exceed that of an open surgical approach.

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BIPOLAR HOOKED-WIRE ELECTROMYOGRAPHIC TECHNIQUE IN THE EVALUATION OF PEDIATRIC VOCAL CORD PARALYSIS

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Laryngeal electromyography is a valuable test to assess vocal cord paralysis in adults. This technique can be applied and adapted to the pediatric patient. In the operating room under general anesthesia and endoscopic guidance, bipolar hooked-wire electrodes are passed percutaneously through the anterior neck skin into both thyroarytenoid muscles. Electromyographic signals are evaluated during light anesthesia and on awakening. A critical appraisal of this technique is presented, including an analysis of sources of electrical interference in the operating room.

KEY WORDS — adolescent, child, electromyography, implanted electrode, laryngeal muscles, vocal cord paralysis.

INTRODUCTION

Vocal cord paralysis (VCP) is uncommon in children. Although the incidence is not known, in the early age group it is most commonly related to birth trauma, meningomyelocele, Arnold-Chiari malformation, tracheoesophageal fistula, and anomalies of the heart and great vessels. Traditionally, children with suspected VCP have been evaluated by direct laryngoscopy, although most otolaryngologists now prefer flexible fiberoptic laryngoscopy (FFL) to assess laryngeal dynamics.[1] However, even with the use of FFL, VCP may be difficult to diagnose in the young child. Laryngeal electromyography (EMG) can supplement the FFL examination by identifying children with VCP and prognosticating the potential for return of function.

In adults, laryngeal EMG is a valuable adjunct to evaluate the neuromuscular status of the larynx, provide site-of-lesion information, distinguish true paralysis from mechanical dysfunction, and differentiate myopathy from neuropathy.[1-5] In children, however, its use has largely been limited to occasional recordings in older children listed in adult series.[6,7] The only study dealing strictly with children was reported by Koch et al[2] and involved a technique in which monopolar hooked-wire electrodes were placed into the posterior cricoarytenoid muscle under general anesthesia.

We have started to use percutaneous bipolar hooked-wire electrode laryngeal EMG to supplement the evaluation of VCP in selected children. The technique and its application and limitations are described. When perfected, laryngeal EMG may provide prognostic information relevant to the management of the pediatric patient.

TECHNIQUE

All children with suspected VCP are evaluated by video FFL. If the clinical diagnosis of VCP is made, the patient is considered for laryngeal EMG. Criteria for EMG evaluation include 1) symptomatic VCP, 2) recent onset of VCP (less than 12 months), 3) surgical candidacy, and 4) consent of the parents or guardian.

Laryngeal EMG is recorded in the operating room (OR) under general anesthesia, with inhalation agents given via masked ventilation or through an existing tracheotomy tube. No muscle relaxants are used. Once the child is anesthetized, direct laryngoscopy is done to assess passive arytenoid mobility, and then a rigid bronchoscope (with the side ventilating ports occluded with tape) is placed at the laryngeal introitus so that the glottis can be visualized and ventilation can be continued.

Bipolar hooked-wire electrodes (Fig 1) are made by threading a pair of 0.076-mm-diameter insulated

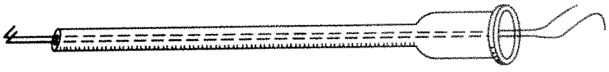

Fig 1. Drawing of bipolar hooked-wire electrode assembly (not to scale).

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Presented at the meeting of the American Society of Pediatric Otolaryngology, Palm Desert, California, April 15-17, 1992.

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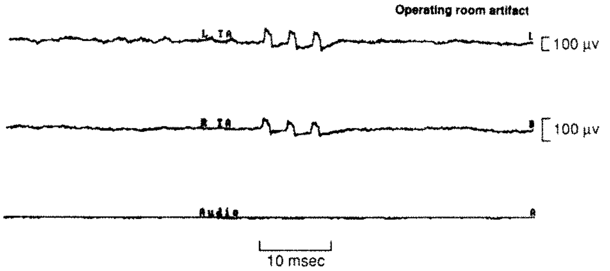

Fig 2. Unusual operating room artifact noted in first 3 cases. This triplet signal appeared simultaneously at irregular rate of about 25 Hz in both channels throughout recording. TA — thyroarytenoid muscle.

stainless steel wires (part 316 SS 3T from Medwire Corp, Mt Vernon, NY) through a 3.8-cm, 25-gauge hypodermic needle. Approximately 1 mm of insulation is mechanically stripped from the end of each wire. A "hook" is formed in each wire by bending it sharply 1.5 to 2.0 mm from its end by using fine jeweler's forceps. The "hooks" then are pulled toward the tip of the needle until they catch on the needle tip. They are inspected with an operating microscope to make sure the bared portions of the wires are not in contact, and the assembly is sterilized.

The needle–hooked-wire electrode unit is passed percutaneously through the cricothyroid space into the laryngeal lumen. Under direct endoscopic observation, the needle then is angled superiorly and laterally into the thyroarytenoid (TA) muscle through the undersurface of the true vocal cords (TVCs). Electrode placement is verified by visualizing the needle tip under the mucosa of the TVCs and by wiggling the needle to deform the TVCs. This is essential if conclusions are to be drawn from the EMG data. When the needle is withdrawn, the hooked-wire electrodes become anchored in the TA muscle. After bilateral placement, electrical activity and an audio signal are recorded.

The child is awakened and a pressure transducer attached to a face mask is used to monitor the respiratory cycle, thereby correlating the EMG recordings with inspiration and expiration. Recordings are made of crying, swallowing, coughing, and, if possible, speech. Once a recording is completed, the electrode wires are gently withdrawn. Patients are monitored for 6 hours before being discharged. No airway problems have occurred.

DATA ANALYSIS

Data are recorded on an instrumentation tape recorder (DC band-pass 2.5 kHz). Analysis is performed on a Hewlett-Packard computer with DATAQ Instruments CODAS (computer-based oscillograph and data acquisition system) software used to display data for assessment of waveform morphology and for measurement of duration, amplitude, and character of muscle response.

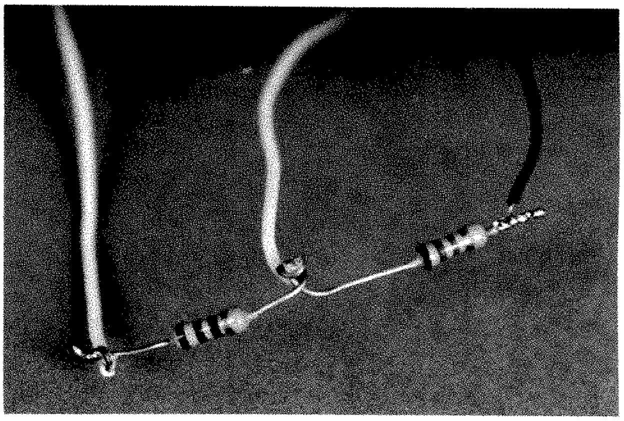

Fig 3. Photograph of pair of 1.8-megaohm, 0.25-W resistors used for electrode "model." Leads to preamplifier were about 1 m long. Center lead goes to reference input (so-called "ground"). Other 2 leads go to inputs of differential amplifier.

Operating room artifacts have presented a difficult problem (Fig 2), and a bipolar electrode "model patient" was constructed by connecting two 1.8-megaohm, 0.25-W resistors from each of the amplifier input leads to the reference lead (Fig 3). The 3 leads were connected to the preamplifier, and the "model patient" was moved about the OR, placed in different positions, and finally left on the operating table to record the different electrostatic potentials in the OR environment.

One constant source of high-frequency artifact was the pulse oximeter. Artifact occurred when the oximeter was in close proximity to the electrodes or when a person was simultaneously touching both the oximeter and the electrode wire. The gas monitor also produced artifact at a rate synchronous to the flickering of the screen. However, this artifact was eliminated when the electrode model was moved away from the anesthesia equipment and placed on the operating table (a distance of about 1 m).

If a person was positioned between the anesthesia equipment and the operating table, artifact was again observed, secondary to the conductive effect of the human body. By keeping all equipment a reasonable distance from the electrodes and minimizing the number of people in the OR, artifact was reduced considerably. We would recommend that these observations be verified at other institutions prior to patient testing.

CASE REPORTS

Case 1. A 41-week, term infant born by an

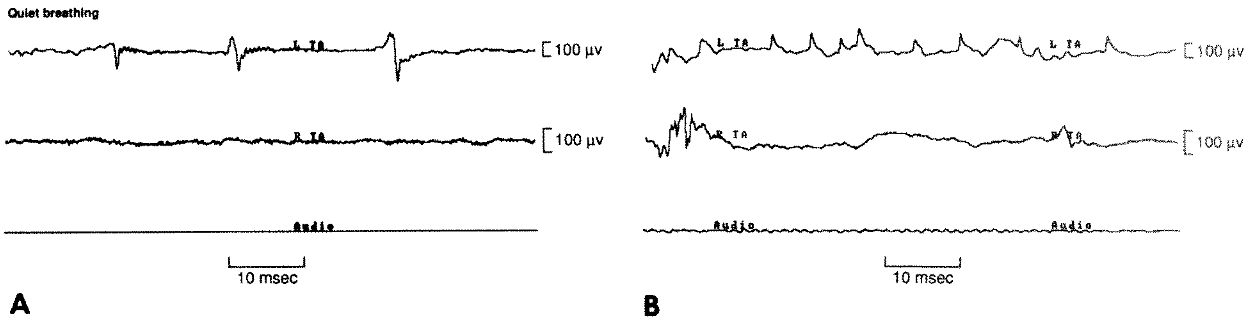

Fig 4. (Case 1) A) During quiet breathing there is activity in left thyroarytenoid muscle (TA). Despite higher gain, no clear activity is observed in right TA. B) Positive sharp waves are seen for left TA. Note irregular pattern of activity, occurring at high frequency and lasting short period.

uncomplicated spontaneous vaginal delivery was transferred to our institution for an evaluation of a weak cry, suprasternal retractions, and worsening perioral cyanosis. Although he had a vigorous suck and was able to breast-feed without difficulty, FFL revealed an immobile right TVC and paresis of the left TVC. There were no abnormalities of the brain, neck, or mediastinum by magnetic resonance imaging.

Laryngeal EMG was performed to establish whether any electrical activity was present in the right TVC. Intermittent single motor unit (SMU) activity (Fig 4A) was documented in the left TA muscle with quiet breathing. Some positive sharp waves also were seen (Fig 4B). There was no definitive EMG activity noted in the right TA muscle. These findings suggest that an injury to both recurrent laryngeal nerves occurred prior to birth and that left TVC function should improve.

The left TVC subsequently recovered sufficiently to obviate tracheotomy. Prognosis for recovery of the right TVC is unknown. The patient will be followed up by FFL.

Case 2. A 14-year-old girl with a history of a medulloblastoma treated by surgical extirpation as well as postoperative radiotherapy and chemotherapy presented to our service in severe respiratory distress. The FFL demonstrated bilateral VCP with paradoxical TVC movement. Computed tomography of the head confirmed the diagnosis of acute hydrocephalus, and a ventriculoperitoneal shunt revision was performed by the neurosurgical service after airway control was established by tracheotomy.

Laryngeal EMG was performed 4 weeks after the onset of symptoms. Recordings were made during quiet breathing under general anesthesia and on awakening. Activity also was monitored during swallow, awake breathing, and phonation.

The EMG signal showed SMU activity in the left TA muscle with swallowing and phonation (Fig 5). There was SMU activity in the right TA muscle as well, although not of the same frequency as that seen on the left. The SMU activity suggested a good prognosis. Recovery of bilateral TVC mobility returned 2 months later and the patient was decannulated.

Case 3. A 3-year-old boy with complex congenital heart disease (tetralogy of Fallot, pulmonary atresia, and ventricular septal defect) was referred for symptoms of hoarseness, clinical aspiration, and biphasic stridor following a right Blalock-Taussig shunt. A left Blalock-Taussig shunt had been performed 1 year earlier. Examination was remarkable for a right Horner's syndrome, left TVC paresis, right TVC paralysis, and a type 1 laryngotracheoesophageal cleft.

On the basis of the severity of symptoms and these physical findings, a tracheotomy was recommended. However, the parents refused this option and so laryngeal EMG was performed to establish whether there was any electrical activity in the right TVC. Recordings were made during quiet respiration under anesthesia and with coughing and crying on awakening.

The SMU activity in the left TA muscle was consistent with a resting breathing pattern (Fig 6). Analysis of EMG data showed no clear evidence of SMU activity in the right TA muscle, although there was low-amplitude, low-frequency activity, presumably recorded from distant muscles. These results suggested that right TVC function would not improve, and a tracheotomy was performed.

Case 4. A 10-month-old girl born prematurely required intubation from birth to day of life 29. Following extubation, she exhibited positional stridor and a weak cry. Her history also was remarkable for ligation of a patent ductus arteriosus. The FFL revealed an immobile left TVC (day of life 77). Because of the positional stridor and hoarseness, laryngeal EMG was done to establish the nature of the

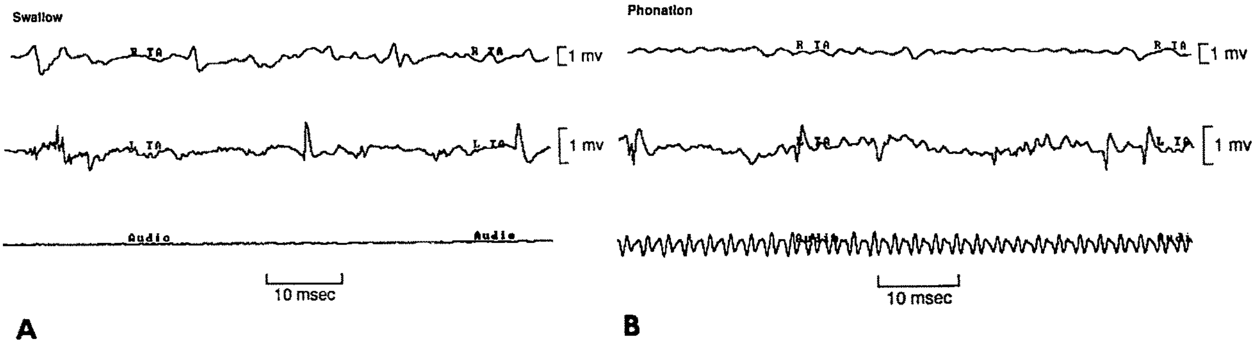

Fig 5. (Case 2) Single motor unit activity apparent in both left and right thyroarytenoid muscles (TA), associated with A) swallow and B) phonation. Activity was more consistent throughout recording in left TA.

injury to the left recurrent laryngeal nerve.

The SMU activity demonstrated in the right TA muscle (Fig 7) was consistent throughout the recording and varied appropriately with respiration and cry. There was no evidence of normal SMU activity in the left TA muscle, although occasional small potentials unrelated to breathing or crying were observed. These findings suggest that the prognosis for return of left TVC motion is poor. No further treatment is planned at this time.

COMMENT

Vocal cord paralysis is infrequent in newborns and small children, but when it does occur, it can be disabling.[8-10] The symptoms are generally those of upper airway obstruction and include intermittent stridor, a weak cry, aspiration, and dyspnea. The severity of the symptoms depends on the nature of the paralysis and the presence of associated conditions.

Recent reports suggest that the diagnosis of VCP in children is increasing.[1,11] This probably reflects improvement in diagnostic capabilities and increased survival of infants and children with more severe medical problems. However, although the problem is more readily recognized, few prognostic or therapeutic advances have been made. For example, the appropriate length of time to wait before concluding that paralysis is permanent is based on clinical observation. Recommendations range from 6 months to 6 years.[9,12-15] In adults, in contrast, the recommended period of observation is 6 to 12 months.[16]

Laryngeal EMG may provide valuable prognostic information. The degree of paralysis can be quantitated, progressive denervation can be documented, and signs of an incipient recovery can be detected. This information could aid therapeutic decision-making. However, pediatric laryngeal EMG has been impractical for 2 reasons. First, accurate electrode placement is of paramount importance. Usually, placement is confirmed by asking patients to phonate — clearly an impossibility in children, because general anesthesia must be used. Second, if general anesthesia is to be safely administered, particular equipment is required. The electrical noise this equipment generates interferes with the sensitive instruments used to record laryngeal muscle activity.[17]

The percutaneous technique we use effectively deals with the first problem, and by "searching" the operating room for various sources of electrical noise, the effect of interference can be minimized. Percutaneous electrode placement was reported initially by Fink et al,[18] who identified the cricothyroid and TA muscles by reference to landmarks on the laryngeal skeleton. Hiroto et al[19] standardized a technique to reach all the internal laryngeal muscles percutaneously; however, we prefer the simpler method described by Shipp et al.[20] By this technique, the electrode needle is passed into the laryngeal lumen, rather than submucosally, and directed into the TA muscle under direct endoscopic observation. Electrode placement is verified visually, by wiggling the needle after the TVC has been impaled and observing the TVC for movement.

We studied only the TA muscle in our patients; for most laryngeal abnormalities in which paralysis is present or suspected, it is not necessary to sample additional muscles within the recurrent laryngeal nerve distribution. Bipolar hooked-wire electrodes

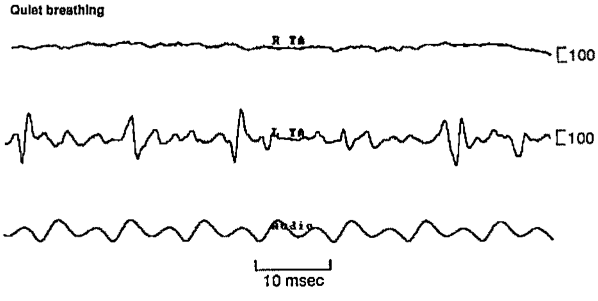

Fig 6. (Case 3) Single motor unit activity in left thyroarytenoid muscle (TA), associated with breathing. No activity was observed in right TA throughout recording period. Waveform in audio record is caused by stridor.

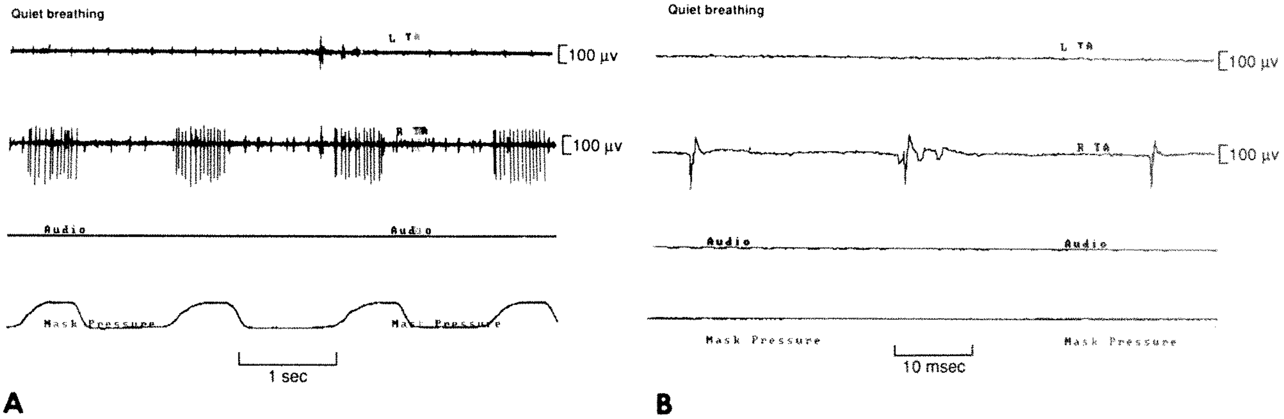

Fig 7. (Case 4) A) Single motor unit activity in left thyroarytenoid muscle (TA), associated with expiratory phase of respiration, represented by positive (upward) mask pressure. B) Expanded view showing single motor units in left TA.

are used because of their flexibility and recording properties. The flexibility of wire electrodes minimizes the possibility of extrusion despite movements from coughing, crying, and swallowing. It also reduces trauma and microphonic and movement artifact.[21] The technical advantages of bipolar electrodes that affect recording properties include more precise localization of electrical activity and fewer cross talk potentials from nearby muscle when compared with monopolar electrodes.[22]

Most of the SMU activity we observed occurred during expiration — a finding that correlates well with other reports. Nakamura et al[23] have shown that the frequency of adductor impulses is greatest at the start of expiration, gradually drops as expiration continues, and is zero at the end of expiration. Although fibrillation potentials tend to appear 1 to 3 weeks following neurogenic injury, they are difficult to detect if there is background noise.

In 3 of 4 patients, significant artifact was encountered. Performing the EMG recordings in the OR contributed to this problem, because the environment could not be manipulated to control 60-Hz and other electrical interference. However, we have studied the OR equipment to identify and minimize sources of artifact.

Pediatric laryngeal EMG still cannot be used to determine topognosis, because standard verification procedures, such as pitch range for the cricothyroid muscle, cannot be used in an uncooperative patient, and surgical verification of position is unwarranted. Evoked laryngeal EMG ultimately may circumvent this problem. Normative data in pediatric patients also are lacking, and until recordings are reported in normal laryngeal muscles over the pediatric age range, this will be a source of uncertainty.

In summary, 1) laryngeal EMG can be done in pediatric patients, 2) it may offer prognostic information, 3) general anesthesia is required, 4) electrode placement must be verified by direct observation, 5) a percutaneous approach directly into the inferior surface of the TA muscle is technically easy and reliable, and 6) sources of OR artifact must be studied to minimize electrical interference.

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TWENTY-NINTH POSTGRADUATE COURSE IN EAR SURGERY

The 29th Postgraduate Course in Ear Surgery will be held April 10-15, 1994, in Nijmegen, the Netherlands. For more information, contact Prof dr P. van den Broek, University Hospital Nijmegen, Department of Otorhinolaryngology, PO Box 9101, 6500 HB Nijmegen, the Netherlands; fax 80-540251.

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FIRST CONGRESS OF EUROPEAN SKULL BASE SOCIETY

The European Skull Base Society will hold its first congress September 26-30, 1993, in Riva del Garda (Trento), Italy. For further information contact Carmelo Zappone, MD, Congress Secretary, Division of ORL, Ospedali Riuniti, Largo Barozzi 1, 24100 Bergamo, Italy; telephone 35-269578; fax 35-269460.

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GIANT SUPRASTOMAL GRANULOMA AS A LARYNGEAL MASS

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The presence of suprastomal granulomas after tracheotomy is a common occurrence. Under most circumstances, this never becomes clinically relevant. However, in the pediatric population, granulomas can on occasion cause partial or complete airway obstruction after decannulation. This report describes 2 cases of giant suprastomal granulomas that presented as laryngeal masses. These cases stress the indications for routine endoscopic evaluation in patients with long-term tracheotomies. Also, the treatment of extensive suprastomal granulomas requires open excision, which differs from the endoscopic approach recommended for smaller granulomas.

KEY WORDS — granuloma, tracheotomy.

CASE REPORTS

Case 1. An 18-month-old boy presented with a diagnosis of cerebral palsy and bilateral vocal cord paralysis. Tracheotomy had been performed 6 days after birth. Several attempts to place a Passy-Muir speech valve had been unsuccessful. The patient's family presented to the pediatric otolaryngology clinic at the University of Michigan to inquire about the possibility of decannulation.

His medical history included a seizure disorder that was being treated with Dilantin. His surgical history included a gastrostomy tube placement and a gastric fundoplication procedure.

Initial examination revealed a well-nourished child with a No. 2 pediatric Shiley tracheotomy tube in place. Flexible laryngoscopy was inconclusive secondary to excessive hypopharyngeal secretions.

The patient was then scheduled for direct laryngoscopy, bronchoscopy, and laryngeal electromyography (EMG) to evaluate vocal cord function. However, on direct laryngoscopy, the patient was found to have a large, pale mass filling and obstructing the glottis and extending into the supraglottic region (Fig 1). The mass was submitted to biopsy and laryngeal EMG was then performed, revealing action potentials in both posterior cricoarytenoid muscles. Subsequent evaluation included a neck computed tomography (CT) scan that demonstrated a large, nonenhancing mass filling the endolarynx and subglottic region (Fig 2). The histologic specimen was read as scar tissue with no evidence of neoplasm. On the basis of these findings, the mass was felt to represent a large, well-organized suprastomal granuloma. The patient subsequently underwent an open excision through a low laryngotracheofissure. A midline incision of the tracheal rings proximal to the tracheotomy tube was extended through the cricoid cartilage and the lower third of the thyroid cartilage, providing excellent visualization of the mass (Fig 3). After delivery of the endolaryngeal portion through the true vocal cords, the mass was freed from its attachment at the anterior-superior lip of the tracheotomy site (Fig 4). The cartilage was reapproximated with interrupted 4-0 Vicryl sutures, and the neck incision closed primarily.

The postoperative course was uncomplicated and the final pathologic diagnosis was unchanged from the initial biopsy. Repeat endoscopy 2 months after the excision revealed a patent subglottic airway and

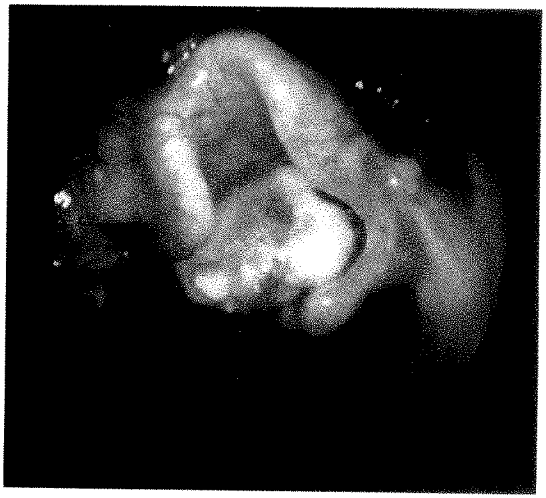
Fig 1. (Case 1) Mass filling endolarynx as viewed on direct laryngoscopy.

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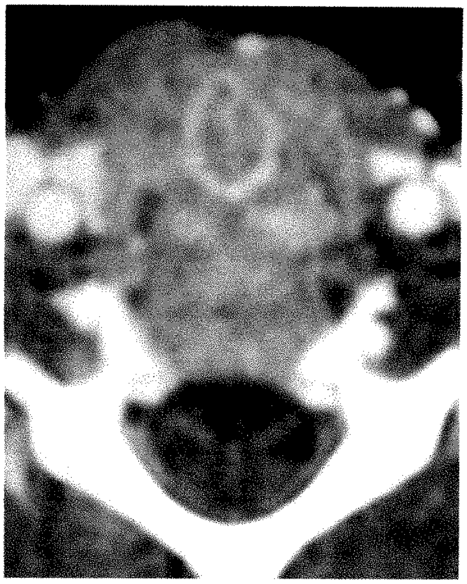

Fig 2. (Case 1) Axial computed tomogram demonstrating nonenhancing mass with outer calcific layer filling airway.

the tracheotomy tube visible below (Fig 5).

Case 2. A 22-month-old boy was referred to the Department of Pediatric Otolaryngology and Maxillofacial Surgery at the University of Cincinnati for evaluation of an obstructing laryngeal mass. The child was born prematurely at 29 weeks and developed bronchopulmonary dysplasia that required long-term ventilator support. Tracheotomy was performed at 2 months of age. After being weaned from the ventilator, the patient had persistent severe reactive airway disease that resulted in frequent hospital admissions. On a recent admission, flexible bronchoscopy demonstrated a large, glistening mass filling the endolarynx. The distal (toward the center of the patient) tracheobronchial tree was normal. The patient was referred for evaluation of the mass.

On examination, the child developed mild expiratory stridor when agitated. A No. 5 Argyle tracheotomy tube was in place. Flexible laryngoscopy revealed a large, white mass filling the endolarynx. Further preoperative workup included anteroposterior and lateral neck films that revealed no air shadow in the subglottic area and down to the tracheotomy site.

Microlaryngoscopy and bronchoscopy revealed a large, firm, white mass filling the endolarynx (Fig 6). The mass filled the glottis, and the subglottis could not be visualized. The distal (toward the center of the patient) trachea as viewed through the tracheotomy site was completely normal.

Excision of the mass was performed through a midline vertical laryngotracheofissure. The mass was removed from its attachments at the anterior-superior aspect of the tracheotomy site. The histologic specimen was read as polypoid, edematous, collagenized connective tissue covered with squamous and respiratory epithelium. The postoperative course was unremarkable. Repeat endoscopy at 2 months revealed persistent subglottic edema.

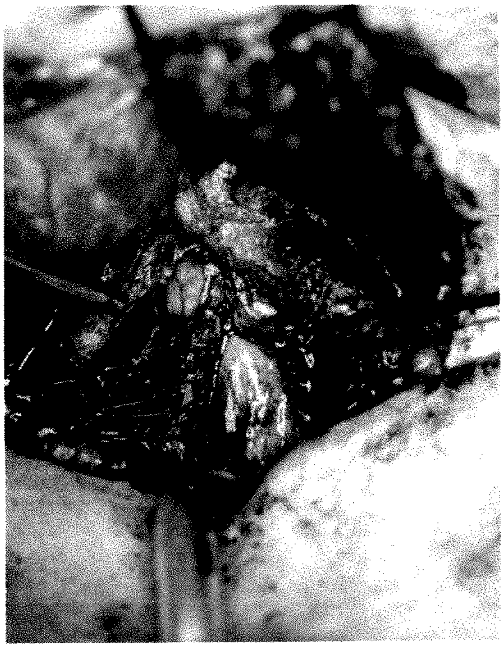

Fig 3. (Case 1) Approach to mass through low laryngotracheofissure with mass filling subglottis.

DISCUSSION

Suprastomal granulomas are a common occurrence in association with tracheotomy as the operative site heals by secondary intention. Within the lumen of the trachea, the most frequent location of this tissue is along the anterior-superior edge of the tracheotomy site.[1] Reilly and Myer[2] have estimated that granulomas can be found in this suprastomal area in approximately 50% of children with a tracheotomy tube in place for more than 4 weeks. This site is predisposed to repeated trauma as it becomes the point of contact between the trachea and the tracheotomy tube during flexion of the neck. Siddharth and Mazzarella[3] have made the association between fenestrated tracheotomy tubes and suprastomal granulomas, believing that the anteriormost fenestration of the tube can abrade the suprastomal trachea and induce granuloma formation. Other irritants that might predispose to granuloma formation include infection,[1] poor humidification,[1] and gastroesophageal reflux.

Although the overall occurrence of suprastomal granulomas may be quite high, the incidence of large granulomas is much lower. Tucker and Silberman[4] reviewed the world literature on pediatric tracheotomies in 1972 and found only 18 in 4,000 (0.45%)

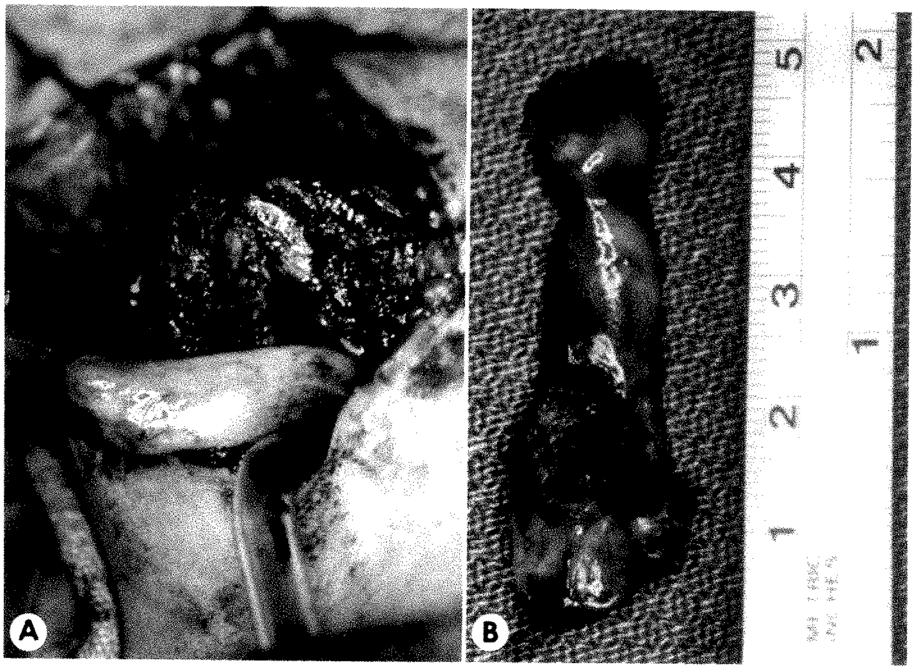

Fig 4. (Case 1) A) Mass delivered from larynx but attached at superior lip of tracheotomy site. B) Excised mass measuring 5 cm in length.

complicated with granuloma, 2 in 4,000 resulting in death. A number of reviews exist within the literature describing small series of large suprastomal granulomas.[5-8] In many of these cases, the granulomas are recognized after unsuccessful attempts at decannulation, or by increasing airway compromise evolving at variable times after decannulation. Reilly and Myer[2] pointed out the importance of documenting and treating these lesions prior to decannulation. A soft tissue lateral neck radiograph is recommended as the most useful study to screen for suprastomal granulomas, and routine rigid endoscopy is recommended on all pediatric patients prior to decannulation.[2] In addition to endoscopy prior to decannulation, we feel that endoscopy should be performed on all pediatric tracheotomy patients prior to any change in airway status such as Passy-Muir valve placement, a change in tracheotomy tube size, or tracheotomy tube plugging.

All previous reports of suprastomal granulomas have documented granulomas occurring below the vocal cords. In most cases these granulomas have acted in a ball-valve mechanism to bring about partial airway obstruction. These lesions are typically treated with endoscopic excision. Several reports in the literature also describe larger granulomas that grew circumferentially around the tracheotomy tube in a sleevelike fashion.[5,9] For these larger granulomas, open removal was performed. The 2 cases above illustrate another growth pattern for large suprastomal granulomas, and again illustrate the need for an open

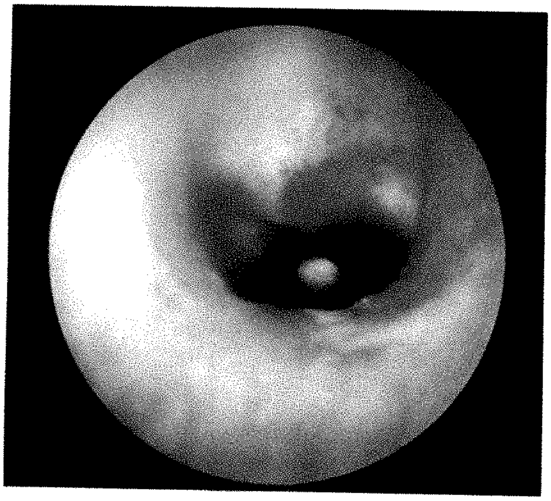

Fig 5. (Case 1) Two-month postoperative view of subglottis, with tracheotomy tube visible distally.

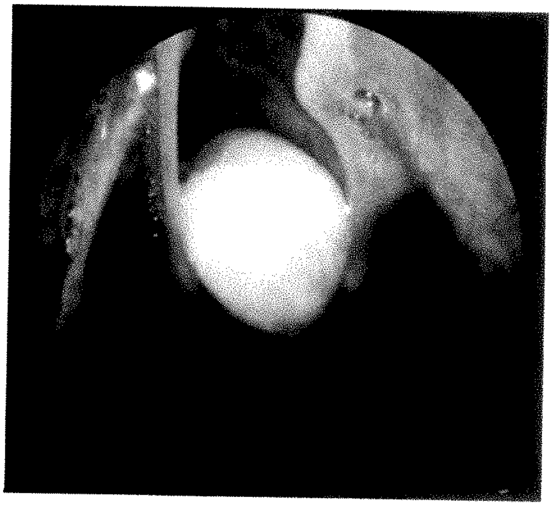

Fig 6. (Case 2) Mass filling endolarynx as viewed on direct laryngoscopy.

excision. We feel that endoscopic removal of such large lesions could easily cause bleeding in the airway that would be difficult to control. The method of "low laryngofissure" (which involves division of the tracheal rings proximal to the tracheotomy site, the cricoid, and the lower third of the thyroid cartilage) offers good visualization without disruption of the anterior commissure.

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DEVELOPMENT OF THE PARANASAL SINUSES IN CHILDREN: IMPLICATIONS FOR PARANASAL SINUS SURGERY

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The pediatric nasal cavity and paranasal sinuses, when compared to those in adults, differ not only in size but also in proportion. Knowledge of the unique anatomy and pneumatization of children's sinuses is an important prerequisite to understanding the pathogenesis of sinusitis and its complications. It is also important in evaluation of radiographs and in planning surgical interventions. In order to study the development of the paranasal sinuses in children and relate clinical anatomy to sinus surgery, the sinuses in 102 pediatric skulls and cadaver heads were measured. The results were classified by stage of development into 4 different age groups: newborn and 1 to 4, 4 to 8, and 8 to 12 years. The characteristics of each group and their clinical importance for paranasal sinus surgery are described.

KEY WORDS — development, nasal cavity, paranasal sinuses.

INTRODUCTION

When reviewing the literature concerning sinusitis in children, it becomes evident that only a few authors have dealt with the development of the paranasal sinuses. In some instances controversial results, not related to clinical findings and experience, seem to have been taken as true and perpetuated from author to author.

Knowledge of the unique anatomy of the nose and paranasal sinuses is a prerequisite to understanding the pathogenesis of sinusitis in children and its complications. Furthermore, it is important for evaluating their radiographs, planning surgical intervention, and especially for avoiding complications. Since the functional endonasal endoscopic surgical approach for chronic sinus disease has become the procedure of choice in adults and children, reliable anatomic descriptions are necessary to make this procedure safe and to minimize risks for the patient.[1-4]

MATERIALS AND METHODS

One hundred two pediatric specimens were examined. There were dried skulls from 38 newborns, 20 children 1 to 4 years old, 23 children 4 to 8, and 13 children 8 to 12. There were preserved cadaver heads from 8 newborns.

Radiographs were taken of all dried skulls (occipitofrontal, occipitonasal, and lateral) to display the paranasal sinuses and their development. Endoscopy of the dried skulls was performed with Hopkins telescopes (Karl Storz GmbH & Co, Tuttlingen, Germany). The preserved newborn cadaver heads were sectioned.[5] One side was dissected in the frontal plane, the other side in the sagittal plane. They were investigated under the microscope. Direct measurements were made of the various sinuses from both the dried skulls and the preserved cadaver heads.

RESULTS

In order for the data to be more useful the specimens were divided into 4 different groups by age: newborn, age 1 to 4, age 4 to 8, and age 8 to 12. The length measurements were ventrodorsal, the height measurements cephalocaudal, and the width measurements mediolateral.

Newborn. In this stage, the lateral nasal wall contains very bulky turbinates (Fig 1A). Most specimens have a superior turbinate. The inferior, middle, and superior meatus are so constricted by the bulk of the turbinates that they are not a functioning part of the respiratory cavity. The free margin of the vomer is in a nearly horizontal position. The eustachian tube ostium is found behind the posterior end of the inferior turbinate, at the level of the hard palate. The uncinate process, hiatus semilunaris, and bulla ethmoidalis have developed and can always be found in a consistent location under the middle turbinate. (Fig 1B,C). The ethmoid sinus system is 8 to 12 mm long, 1 to 5 mm high, and 1 to 3 mm wide. The anterior and posterior ethmoid cells are almost completely developed in number. They are still underdeveloped in

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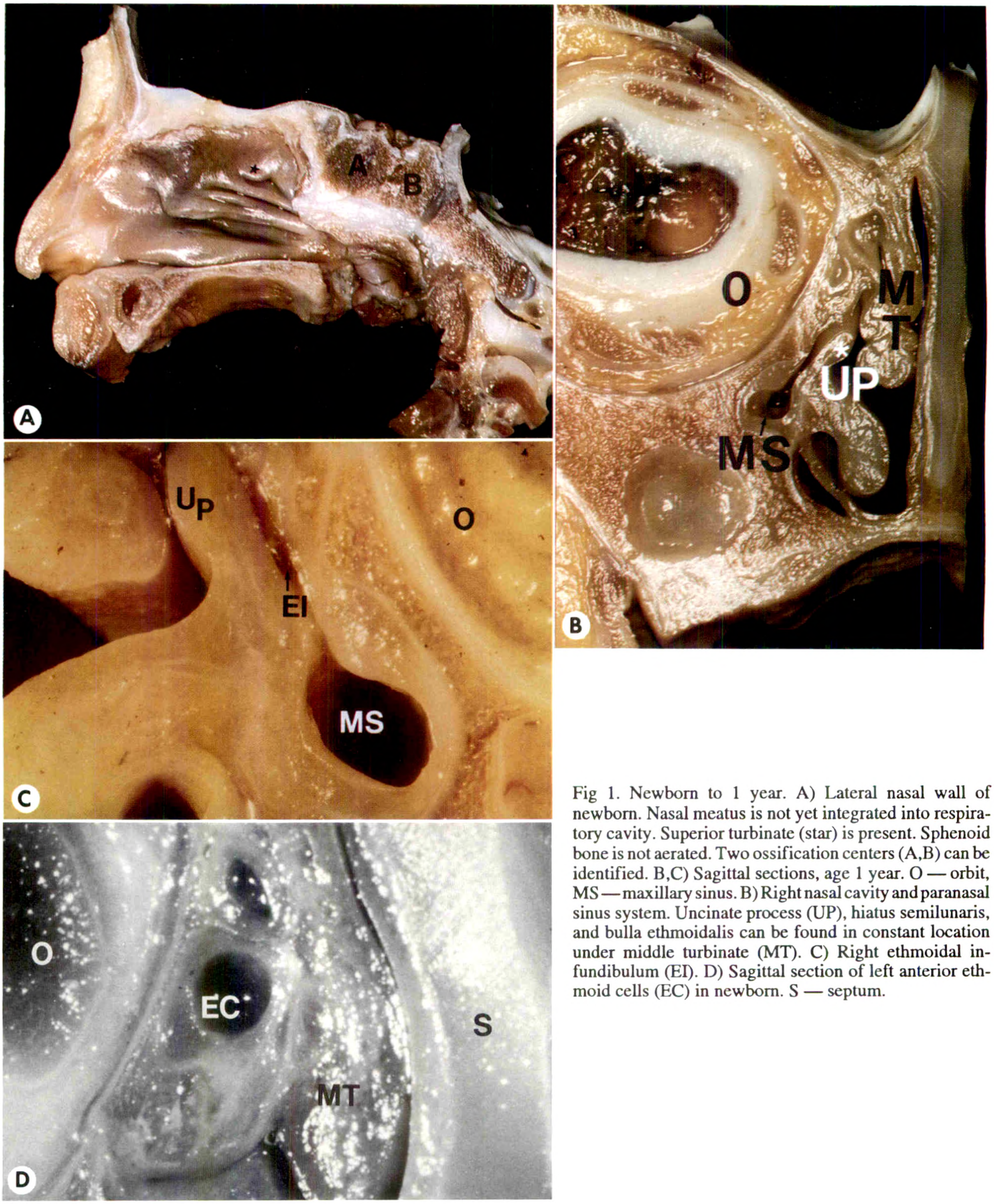

Fig 1. Newborn to 1 year. A) Lateral nasal wall of newborn. Nasal meatus is not yet integrated into respiratory cavity. Superior turbinate (star) is present. Sphenoid bone is not aerated. Two ossification centers (A,B) can be identified. B,C) Sagittal sections, age 1 year. O — orbit, MS — maxillary sinus. B) Right nasal cavity and paranasal sinus system. Uncinate process (UP), hiatus semilunaris, and bulla ethmoidalis can be found in constant location under middle turbinate (MT). C) Right ethmoidal infundibulum (EI). D) Sagittal section of left anterior ethmoid cells (EC) in newborn. S — septum.

size, with significant connective tissue found between the cells (Fig 1D). The frontal sinus has not yet pneumatized the frontal bone. "Cellulae ethmoidales" can be found originating from the ethmoidal infundibulum. These are bony cells or indentations pneumatizing toward the frontal bone, not yet having reached it. Kasper[6] described these as a series of 4 frontal pits or furrows. The first generally becomes the agger nasi cell, the second the frontal sinus, and the third and fourth the various anterior ethmoid cells. The maxillary sinus has a spherical, or in some cases, a pyramidal shape. It is 10 mm long, 4 mm high, and 3 mm wide (Fig 1B,C). The sphenoid sinus in most cases is not developed. However, its ostium occa-

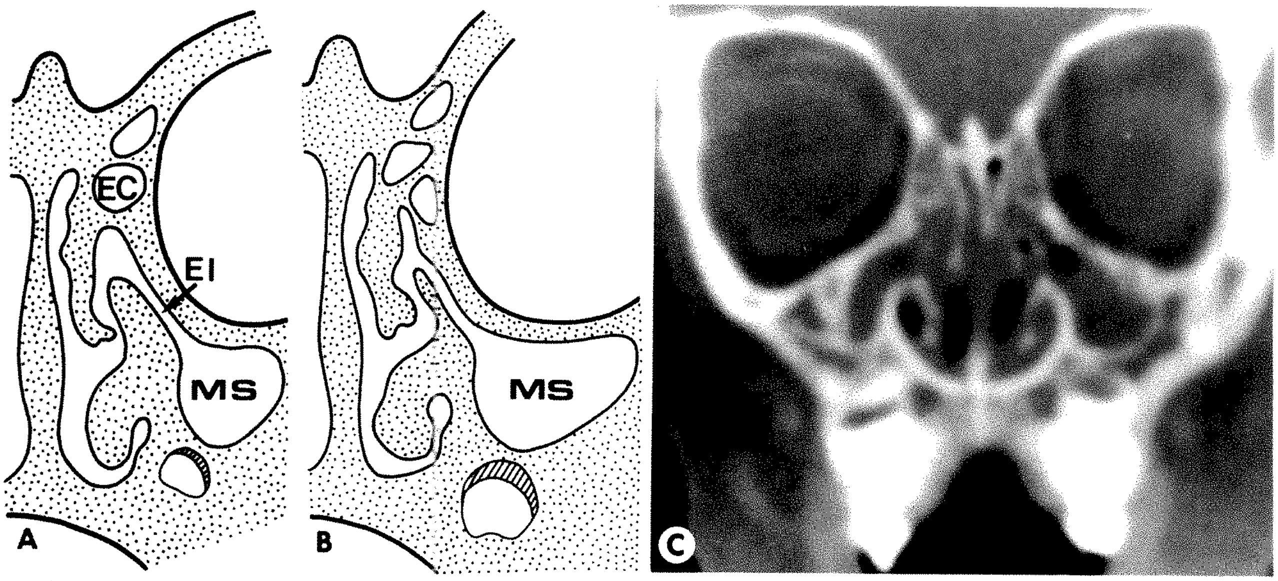

Fig 2. A,B) Left anterior ethmoid cells (EC), ethmoidal infundibulum (EI), and maxillary sinus (MS) in sagittal section. A) Age 4; MS has expanded inferiorly to attachment of inferior turbinate. B) Age 8; MS has expanded inferiorly to middle of inferior meatus. C) Age 8; computed tomogram.

sionally can be identified with a probe. The sphenoid bone consists of 2 bony nuclei, separated by the canalis pharyngeus, which can clearly be identified (Fig 1A).

Ages 1 to 4. The lateral nasal wall contains only 3 turbinates by this age in most of the specimens, indicating that the superior turbinates disappear in the first years of life. By age 4, half of the inferior nasal meatus is developed and integrated into the respiratory cavity. The eustachian tube ostium has reached its definitive position behind the end of the middle turbinate. The ethmoid region rapidly expands. It is 12 to 21 mm long, 8 to 16 mm high, and 5 to 11 mm wide. The frontal sinus starts to pneumatize the frontal bone. It is 4 to 8 mm long, 6 to 9 mm high, and 11 to 19 mm wide. The maxillary sinus also rapidly expands by age 4. Its pneumatization reaches laterally to the infraorbital nerve and inferiorly to the attachment of the inferior turbinate (Fig 2A). A remarkable expansion in length can be found, now measuring 22 to 30 mm. The height is 12 to 18 mm, the width 11 to 19 mm (Fig 2A). The sphenoid sinus pneumatization of the sphenoid bone has begun. It is now 4 to 6 mm long, 3 to 5 mm high, and 6 to 8 mm wide.

Ages 4 to 8. By age 8, pneumatization has progressed considerably (Fig 2B,C). The paranasal sinuses have continued their expansion in all directions. The ethmoid cells have become larger. The ethmoid sinus system is 18 to 24 mm long, 10 to 15 mm high, and 9 to 13 mm wide. The frontal sinus has expanded laterally and medially. It is now 6 to 10 mm long, 15 to 16 mm high, and 8 to 10 mm wide. The maxillary sinus has expanded laterally past the infraorbital canal, and inferiorly to the middle of the inferior meatus. Its shape is tetrahedral, the top pointing to the ethmoidal infundibulum. The length of the maxillary sinus is 34 to 38 mm. It is 22 to 26 mm high and 18 to 24 mm wide. The sphenoid sinus is 11 to 14 mm long, 7 to 11 mm high, and 9 to 11 mm wide.

Ages 8 to 12. At age 12 the nasal cavity and the paranasal sinuses have nearly completed their development, and have reached adult proportions. The choanae have finished their development. They have changed from a circular to a rectangular shape, the height being twice the width. The ethmoid cells are completely developed. The frontal sinus has expanded in length and has become the shape of a tetrahedron. The maxillary sinus has reached the level of the floor of the nose. It has expanded laterally to the molar teeth and zygomatic recess, and medially to the nasolacrimal duct. The sphenoid sinus has reached its permanent size, but not its permanent shape, which is still in development. Its ostium in the sphenoethmoidal recess has an oval shape (Table 1).

DISCUSSION

The fact that the paranasal sinuses in infants and children are different in size and shape from those found in adults is of clinical importance and makes surgery more difficult. Their development is directly linked to the development of the skull and to dentition. In infants the size ratio between the ethmoid and maxillary sinus regions is 2:1; in adults it is 4:5.[7]

In the literature on the development of the paranasal sinuses in children we find numerous variations

TABLE 1. SIZE OF PARANASAL SINUSES IN PRESENT STUDY

Age	*Sinus*	*Length (mm)*	*Height (mm)*	*Width (mm)*
Newborn	Anterior and posterior ethmoid	8-12	1-5	1-3
	Maxillary	10	4	3
1-4 y	Anterior and posterior ethmoid	12-21	8-16	5-11
	Frontal	4-8	6-9	4-7
	Maxillary	22-30	12-18	11-19
	Sphenoid	4-6	3-5	6-8
4-8 y	Anterior and posterior ethmoid	18-24	10-15	9-13
	Frontal	6-10	15-16	8-10
	Maxillary	34-38	22-26	18-24
	Sphenoid	11-14	7-11	9-11

Data are ranges. Where no range is indicated, all measures were identical.

regarding the extent of pneumatization. These are due not only to the individual variations, but also to different techniques of measuring the sinuses and differing opinions about pneumatization at the various ages.

We studied 102 pediatric specimens and our findings concerning the development of the paranasal sinuses were compared to those of Onodi,[8] Koch,[9] Peter,[10] and Grünwald.[11]

Newborn. In the newborn the turbinates are well developed but bulky. Our findings in the dried skulls and preserved cadaver heads support the results of Peter,[10] who described in 88% of newborns a superior turbinate. This superior turbinate is subject to involution; Peter could only identify this structure in 26% of adults. The choana is almost circular, with a diameter of approximately 6 mm. The posterior margin of the septum is in a nearly horizontal position.

Frequently we found a fold of mucosa at the posterior septum, the posterior part of the lateral nasal wall, and the floor of the nose that disappeared before age 4. The nasopharynx of a newborn child is very low, with the eustachian tube ostium found at the level of the hard palate, behind the inferior turbinate. As the paranasal sinuses expand, the hard palate is shifted caudally and the tubal ostium ascends cranially, reaching its definitive position behind the middle turbinate at the age of 4.

The inferior nasal meatus is very narrow and underdeveloped at this age and is not yet integrated into the nasal airway. The same is true for the middle and superior meatus, so that a newborn child breathes through the common nasal meatus. This explains why even a moderate degree of mucosal swelling causes severe nasal obstruction in a newborn. Even with a 2.7-mm rigid telescope, it is not routinely possible to enter the nasal meatus without fracturing the turbinates or producing traumatic lesions of the mucosa.

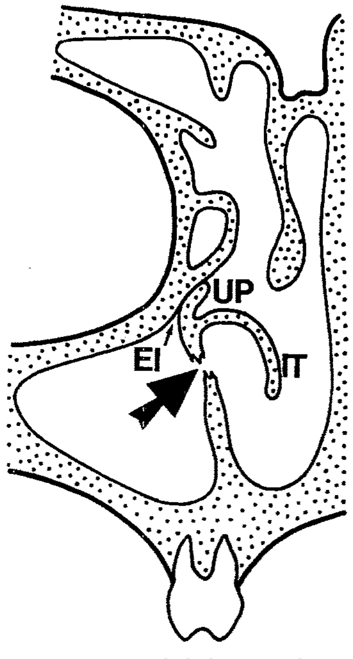

Fig 3. In trying to perform inferior meatal antrostomy, left inferior turbinate (IT) was fractured (large arrow), and uncinate process (UP) was turned laterally, narrowing ethmoidal infundibulum (EI).

The uncinate process, hiatus semilunaris, and ethmoidal bulla are constant landmarks, already well developed in the newborn. The nasolacrimal duct measures about 7.5 mm and ends at the floor of the nasal cavity, right under the head of the inferior turbinate.[10] The organ of Jacobson, representing a 0.2- to 2.5-mm blind duct, can almost always be found in the inferior part of the septum. It subsequently undergoes involution during childhood.[10] The newborn ethmoid cells are well developed and expand rapidly within the next few years at the expense of the connective tissue between them, as we could see by microscopic observations and by following the changes of shape during development. The newborn frontal sinus is just a bony cell, a so-called "frontal cell" draining to the ethmoidal infundibulum. At birth the maxillary sinus represents a shallow sac in the lateral nasal wall.

The sphenoid sinus is a blind mucosal sac that has not yet reached the sphenoid bone or cartilage. The diameter of its ostium measures 0.5 mm. Pneumatization starts at the age of 1, from the posterior ethmoid via the "Bertini bone" (primary pneumatization). It is later integrated into the posterior ethmoid. The body of the sphenoid bone consists of 2 ossification centers: an anterior and a posterior bony nucleus. Between them the "canalis craniopharyngeus"[10,11] can be found.

Ages 1 to 4. In most of the specimens the superior turbinate had disappeared. Half of the inferior nasal

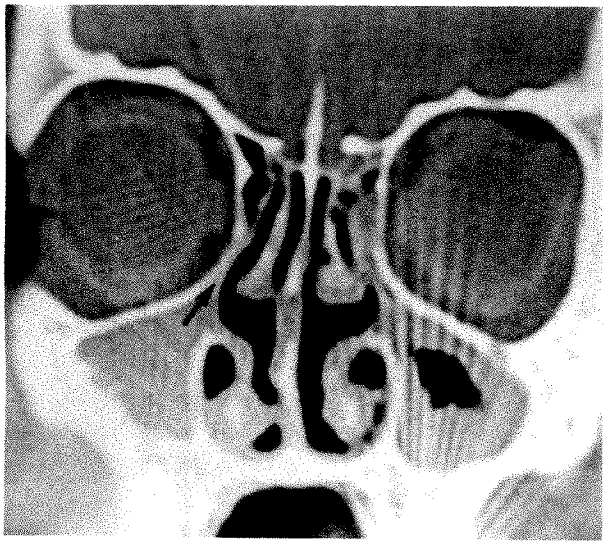

Fig 4. Computed tomogram of 10-year-old child with chronic sinusitis. Right infundibulum is "atelectatic." Uncinate process is attached to lamina papyracea (arrow).

meatus was integrated into the nasal cavity. The top of the eustachian tube ostium was in its definitive position behind the middle turbinate.

The ethmoid sinus expands rapidly a few millimeters in all directions from the first to the fourth years of life. It is well developed in comparison to the other sinuses and is responsible for the frequent orbital complications of sinusitis in childhood. The frontal sinus slowly expands and starts to pneumatize the frontal bone. The maxillary sinus has expanded laterally to the infraorbital canal, and inferiorly to the attachment of the inferior turbinate.[10] Because of the tooth germs, the maxillary sinus still has a spherical shape. The sphenoid sinus at the age of 4 is about the size of a pea (4 to 8 mm in diameter).

Ages 4 to 8. Between the ages of 4 and 8 years the development of the paranasal sinuses is slow. The ethmoid cells expand more slowly than the frontal and maxillary sinuses. The frontal sinus rapidly expands laterally and medially into the frontal bone at the age of 7. The maxillary sinus floor descends to the middle of the inferior meatus by age 7.

Attention must be paid to the tooth buds prior to eruption of the secondary teeth, because they can easily be injured during surgery, ie, Caldwell-Luc procedures, inferior meatal antrostomies, and antral irrigations. The size of the sinuses and the disparity in location of the floor of the nose and the floor of the maxillary sinus in children predispose them to more complications from older, standard procedures than is expected in adults. Maxillary sinus irrigation and antrostomies (nasoantral windows) via the inferior meatus are hazardous, since there may be only spongiotic bone lateral to the floor of the nose.[12] Attempts to penetrate the maxillary sinus from the inferior meatus may fail or end in disaster. Additionally, because of the short medial-to-lateral distance, the lateral wall of the maxillary sinus may be injured with the trocar during antral irrigation. In the creation of nasal antral windows or inferior meatal antrostomies, the inferior turbinate may be fractured medially, which in turn may force the uncinate process laterally, narrowing the infundibulum and creating the conditions conducive to chronic sinusitis[13] (Fig 3). When considering the anatomy at this age and the problems that may occur, it is easy to understand why inferior meatal fenestration in children is not a good idea.

There can also be dangerous situations encountered during middle meatal antrostomy. The uncinate process may be very close to the medial wall of the orbit, so that during uncinate removal the risk of penetrating the lamina papyracea (ie, lamina orbitalis ossis ethmoidalis) with the sickle knife is greatly increased (Fig 4). The orbit may even be entered with the first incision of an endoscopic endonasal procedure. In some cases the attachment of the inferior turbinate is high, narrowing the distance between the uncinate process and the papyraceous lamina. In a situation like this, if an instrument is not introduced precisely during antrostomy, the orbit may also be entered.

Ages 8 to 12. Between the ages of 8 and 12, pneumatization accelerates again. After the eruption of secondary dentition, the maxillary sinus expands, so that the underdeveloped inferior meatus becomes a part of the respiratory cavity and the choanae have changed from circular to rectangular.

The ethmoid cells are so completely developed that there is hardly any connective tissue left between the cells. The proportions of the sinuses become similar to those in adults.

Pneumatization is nearly complete between the ages of 12 and 14, when the floor of the maxillary sinus has reached the level of the floor of the nasal cavity. It expands laterally to the molar teeth and the zygomatic recess, and medially to the nasolacrimal duct. Only a few additional changes can be seen up to the age of 22 or 24, when pneumatization is considered complete.

The sphenoid sinus has reached its permanent size and position, but its shape is still in development (Table 2[8]).

CONCLUSIONS AND CLINICAL SIGNIFICANCE

For diagnosis and surgery it is important to understand that each age has a specific anatomic feature

TABLE 2. SIZE OF PARANASAL SINUSES IN STUDY BY ONODI

Age	*Sinus*	*Length (mm)*	*Height (mm)*	*Width (mm)*
Newborn	Anterior ethmoid	1-5	1-3	1-3
	Posterior ethmoid	2.5-5	4.5-5	1.5-2
	Frontal	3	4.5	2
	Maxillary	2	4	3
	Sphenoid	2	4	2
1 y	Anterior ethmoid	1-9	1-8	1-6
	Posterior ethmoid	2-10	2-8	1.5-8
	Frontal	3.5-8	3-9	2-6
	Maxillary	5-19	3-9	2.5-8
	Sphenoid	1-9	1-5	1-6
1-4 y	Anterior ethmoid	3-8	3.5-11	3-6
	Posterior ethmoid	3.5-11	3.5-10	3-11
	Frontal	6.5	6	5
	Maxillary	26	13	12
	Sphenoid	3.5-5	4.5-6	7
4-8 y	Anterior ethmoid	5-6	8-13	7
	Posterior ethmoid	11-17	6-9	10
	Frontal	4-11	14-17	7-9
	Maxillary	38	23	20
	Sphenoid	12-13	8-12	11

Data from Onodi.[8] Data in ranges. Where no range is indicated, all measures were identical.

concerning the paranasal sinuses.[12] The development of the nose and the paranasal sinuses is directly linked with the development of the facial part of the skull and with dentition.[14] This explains growth disturbances of the facial part of the skull after Caldwell-Luc procedures in children.[15] In our opinion these procedures for chronic sinusitis in the pediatric population are obsolete. Structures of the anterior ethmoid and middle meatus, like the uncinate process, ethmoid infundibulum, hiatus semilunaris, and bulla ethmoidalis, are already well developed in the newborn and are constant findings and good landmarks for surgery, in which special pediatric instruments are required for "atraumatic" and functional surgery.[4]

As the floor of the maxillary sinus is not necessarily at the level of the floor of the nasal cavity, care has to be taken in surgery directed toward the maxillary sinus.[12] This is especially true if the surgery is performed via the canine fossa or the inferior meatus. Because of the anatomic situation of the maxillary sinus, damage can occur to the tooth buds, the spongiotic bone under the floor of the sinus, the lateral wall of the sinus, or the inferior turbinate. So we believe that inferior meatal antrostomies should be avoided, not only for functional, but also for anatomic reasons.

During resection of the uncinate process and enlargement of the natural ostium (middle meatal antrostomy) in functional endoscopic sinus surgery, the orbit may be injured. This is because the inferior turbinate may be located high up on the lateral nasal wall, thus making the anterior margin of the uncinate process close to the papyraceous lamina. Furthermore, the uncinate may be attached to the papyraceous lamina; consequently, during resection the orbit can be penetrated. If these anatomic facts are respected, sinus surgery in the pediatric population may become a safer procedure.

Reports of other authors indicating that the maxillary sinus and ethmoid in newborn and smaller children are just present as rudimentary findings,[16] gaps,[17] or grooves,[18] or not even present,[19] and not developed till early childhood, do not agree with our findings, nor do reports stating that the maxillary sinus is not aerated at birth.[20]

Our experience has shown that in addition to special training and extensive practice in sinus surgery, precise knowledge of the anatomy and development of the paranasal sinuses in children is essential to performing sinus surgery in the pediatric population.

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Ann Otol Rhinol Laryngol 102:1993

ATELECTATIC TYMPANIC MEMBRANE: HISTOLOGIC STUDY

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This study aims to elucidate the morphological difference between the noncollapsible physiologic tympanic membrane (TM) and the collapsible atelectatic TM. Histologic examination of atelectatic TMs obtained at surgery from 16 ears revealed inflammatory changes and destruction of the pars tensa collagenous "backbone." The disappearance of the organized collagenous layer seen in atelectatic TMs explains their conversion from the stiff physiologic membrane to a flexible one. This in turn will convert the middle ear from a noncollapsible gas pocket to a partially collapsible gas pocket, in which minimal pressure of only a few millimeters of water can cause retraction or ballooning of the atrophic TM. These pressure differences are too small to equilibrate automatically the difference created with the atmospheric pressure. Integrity of the pars tensa collagenous layer thus appears to be essential for the proper mechanical functioning of the physiologic TM.

KEY WORDS — biologic gas pocket, middle ear pressure, tympanic membrane.

INTRODUCTION

The main part of the physiologic tympanic membrane (TM), ie, the pars tensa, was described by Bekesy[1] to be relatively stiff, inelastic, and noncollapsible. In contrast, the atelectatic TM is collapsible (Fig 1A). In this histologic study we compare the morphological and structural features of physiologic parts with those of the atelectatic parts of TMs in an attempt to determine the reason for the differences between them in mechanical behavior.

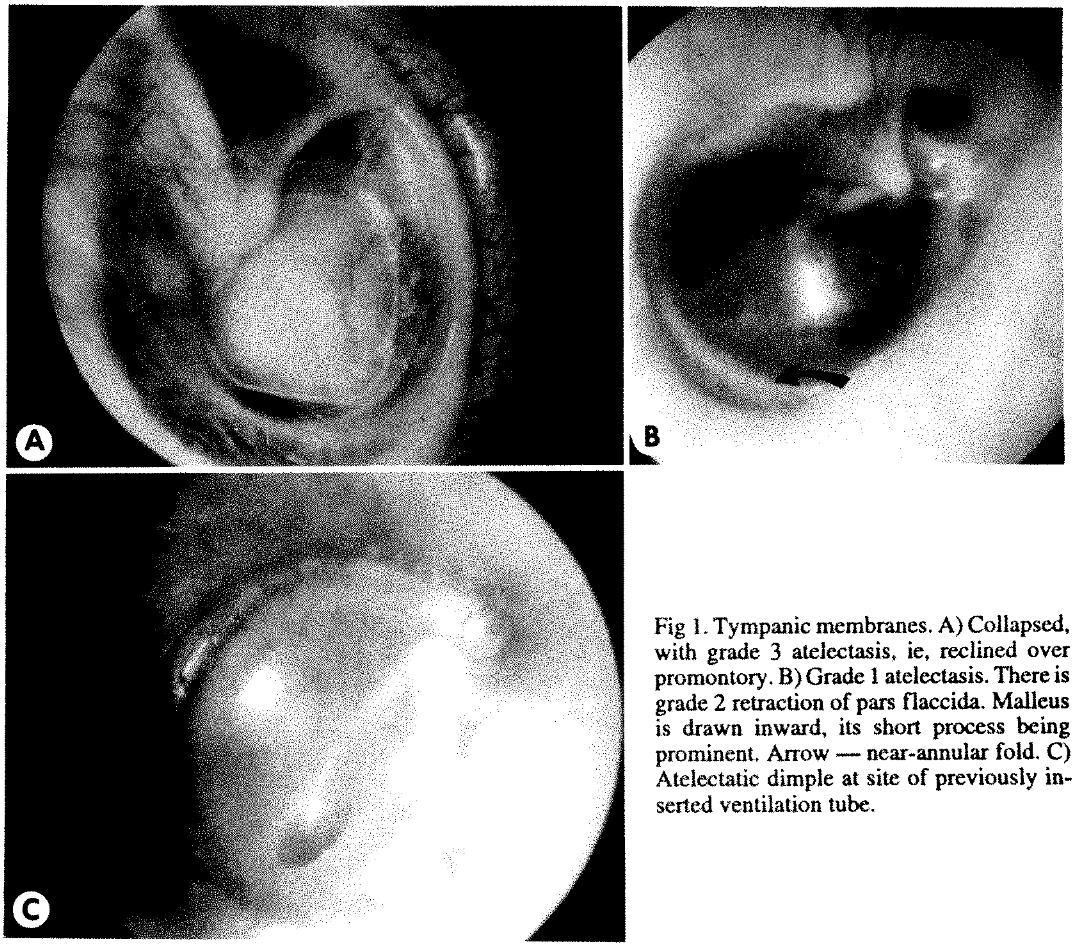

Fig 1. Tympanic membranes. A) Collapsed, with grade 3 atelectasis, ie, reclined over promontory. B) Grade 1 atelectasis. There is grade 2 retraction of pars flaccida. Malleus is drawn inward, its short process being prominent. Arrow — near-annular fold. C) Atelectatic dimple at site of previously inserted ventilation tube.

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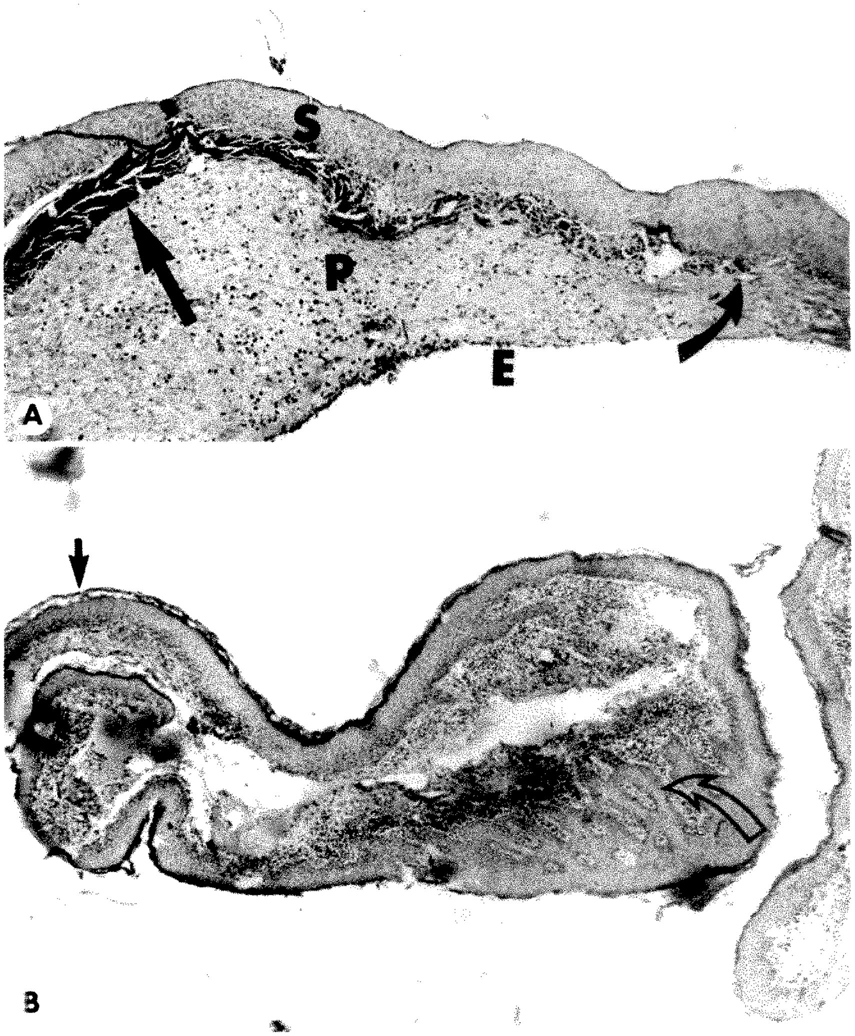

Fig 2. Histograms. A) Pars tensa showing transition of nonatelectatic to atelectatic areas. Note absence of collagenous backbone in atelectatic part (curved arrow) and presence of this organized collagenous structure in nonatelectatic part (straight arrow). E — medial side of middle ear presenting flat epithelium, S — thick squamous epithelium, P — edematous lamina propria infiltrated with round cells. B) Tympanic membrane curled in on itself. Lamina propria is studded with round cells and is devoid of its collagenous layer. Solid arrow — hyperkeratosis on lateral surface, open arrow — papillary formation. (Continued on next page.)

MATERIAL AND METHOD

Sixteen specimens of atelectatic TMs, with some part of the adjacent nonatelectatic pars tensa (Fig 2A), were removed during tympanoplasty from ears with advanced atelectasis (grades 2 through 4).[2] The specimens were fixed in formalin, passed through alcohols and xylol, embedded in paraffin, serially sectioned, and stained with hematoxylin, eosin, and periodic acid–Schiff (PAS) stains. The atelectatic and nonatelectatic parts of the TM were examined histologically and compared.

RESULTS

Atelectatic Part of Tympanic Membrane. The atelectatic areas of the TMs exhibited the following features (Fig 3A).

One was curling of the TM. The straight, linear, "stiff" contour of the physiologic TM was lost in most atelectatic regions, which were found to be curled and folded (Fig 2B).

On the lateral surface of the TM, all specimens showed the outer surface of the atelectatic region to be hyperkeratotic (Fig 2A,B); ie, the amount of keratin was much greater than on the physiologic TM. The squamous epithelium appeared to be thickened (Fig 2) because of the presence of a larger number of cell layers than usual. Various degrees of papillary ingrowth toward the lamina propria were seen (Fig 2B).

The medial epithelium of the TM was flat (Fig 2A,D), and in some places areas of respiratory epithelium were seen. Intracellular PAS-positive granules were abundant. In 5 cases the epithelium was absent, corresponding to the regions of the TM that adhered

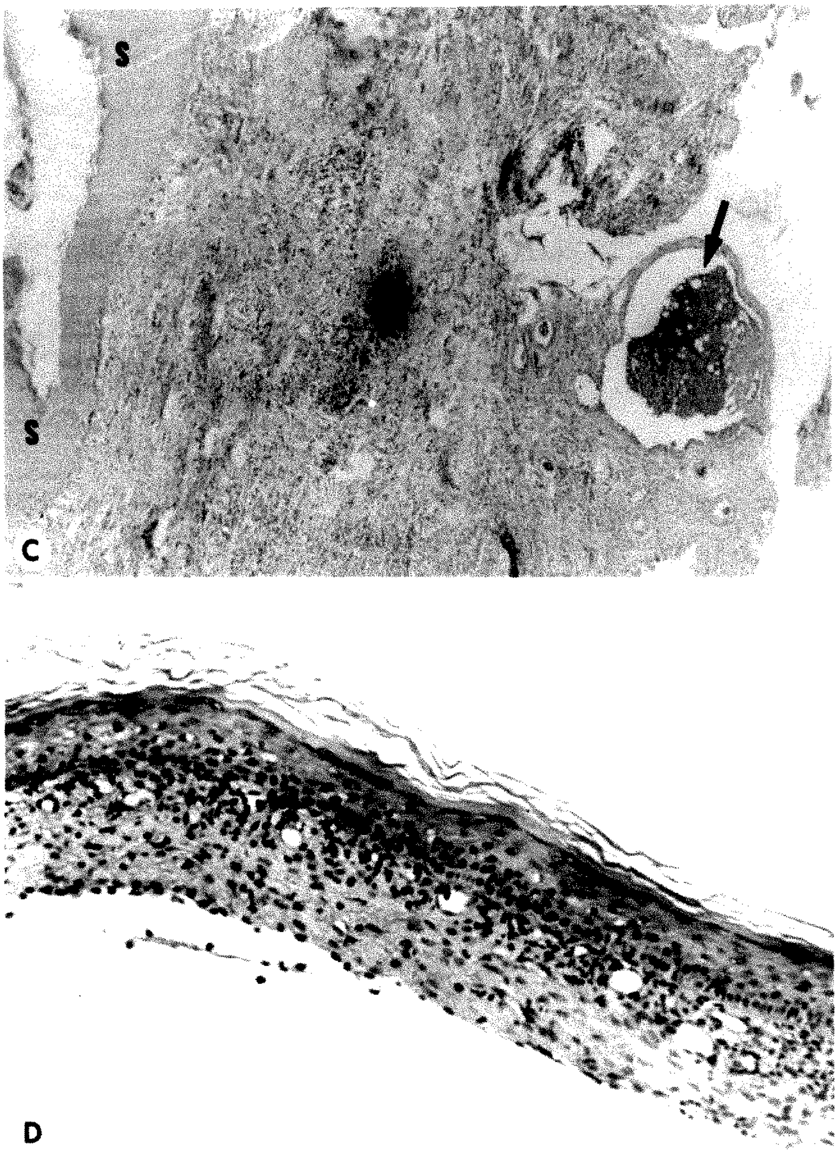

Fig 2, continued. C) Edematous lamina propria, infiltrated with round cells, showing periodic acid–Schiff–positive gland on medial aspect of tympanic membrane (arrow). Collagenous layer is absent. S — lateral squamous epithelium. D) Atelectatic part of tympanic membrane. Lamina propria is totally devoid of collagenous backbone. Round cells are present almost everywhere.

to the promontory.

The lamina propria was edematous. All cases presented impressive infiltration with round cells, mostly lymphocytes and plasmocytes. Scattered PAS-positive glands were seen in 7 of 16 specimens (Fig 2C).

The double collagenous layer of the normal TM, with its typical organized architecture, was absent in all specimens (Fig 2A,D). In 9 cases no collagenous fibers could be detected. Seven specimens contained remnants of collagenous fibers, which were randomly scattered in a nonorganized fashion.

Nonatelectatic Part of Tympanic Membrane. The TM adjacent to the atelectatic part presented the following features (Fig 2A). No curling of the TM was seen. Some degree of hyperkeratosis was present on the medial surface of the TM. The medial side of the TM showed a flat epithelium. In places, islands of respiratory epithelium were also present. The lamina propria presented some edema, as well as some round cell infiltration, in all specimens. Two or 3 very small glands were seen in the lamina propria of 4 specimens. The double collagenous layer was intact in all specimens (straight arrow on Fig 2A).

DISCUSSION

Atelectatic Tympanic Membrane. The major portion of the TM consists of the pars tensa, whose firm structure gives the TM its special mechanical character and accounts for its stiffness, as pointed out by Bekesy.[1] Bekesy, who stressed the inelastic properties of the pars tensa, explained that the physiologic movements of the TM are executed by its moving as a "unit" when it pivots, mainly on its peripheral fold, ie, the "near-annular fold" (Fig 3B[1]). Similar movements of the TM, although of much higher amplitude, can be also observed under the microscope by the use

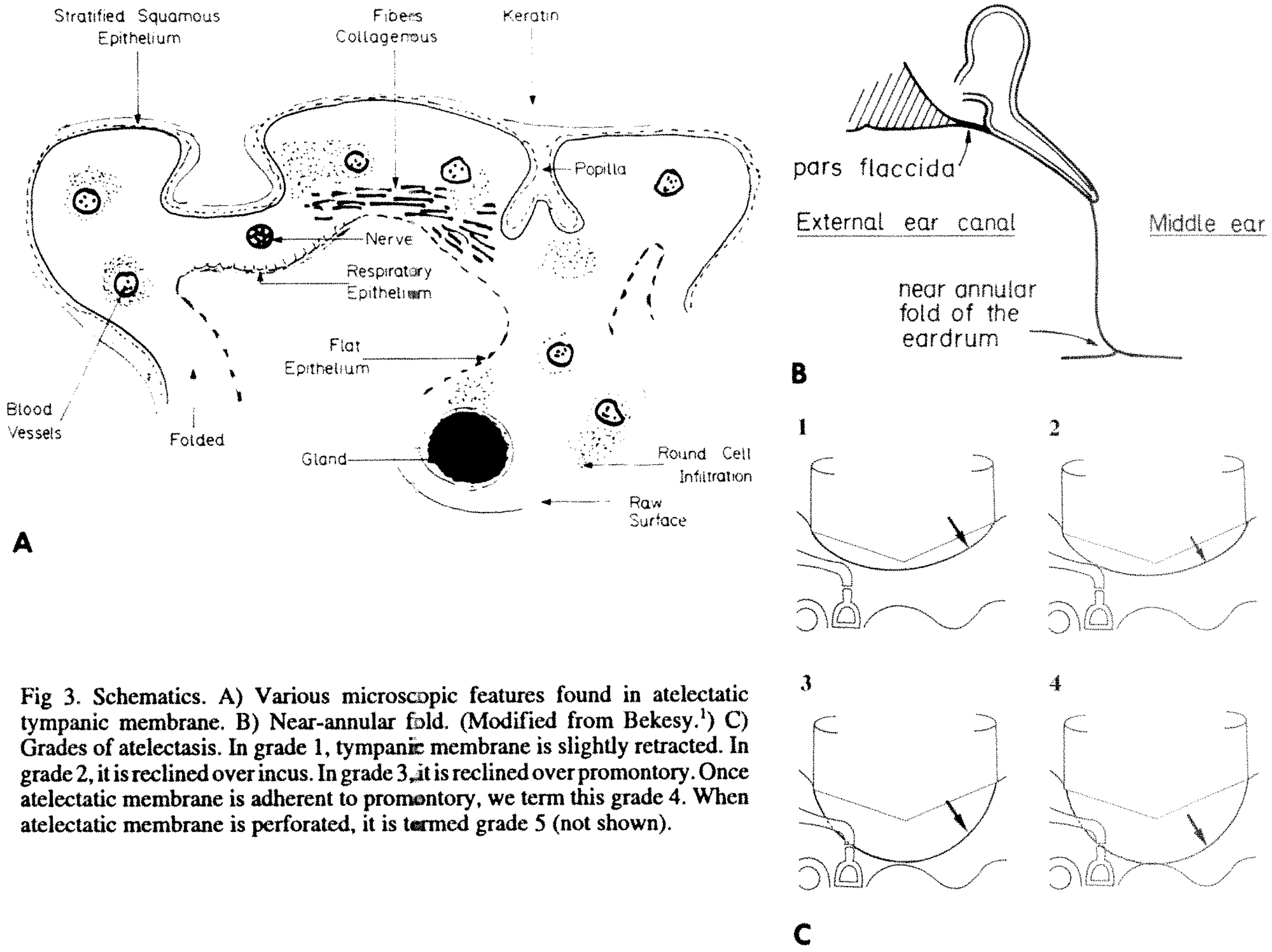

Fig 3. Schematics. A) Various microscopic features found in atelectatic tympanic membrane. B) Near-annular fold. (Modified from Bekesy.[1]) C) Grades of atelectasis. In grade 1, tympanic membrane is slightly retracted. In grade 2, it is reclined over incus. In grade 3, it is reclined over promontory. Once atelectatic membrane is adherent to promontory, we term this grade 4. When atelectatic membrane is perforated, it is termed grade 5 (not shown).

of a Siegel pneumatoscope, in which the magnifying glass is replaced by ordinary, nonmagnifying glass. More complex movements of the pars tensa were observed by Khanna and Tonndorf,[3] using refined hologram techniques.

Atelectasis, or retraction of the pars tensa, was divided by us[2] into 4 categories (Fig 3C) according to the severity of retraction of the TM. Grade 1 atelectasis is usually the result of a slight retraction of the central portion of the pars tensa pivoting around the peripheral, flexible near-annular fold (Fig 1B). This stage is most often transitory.[4] When a TM with grade 1 atelectasis reverts back to its physiologic position, its texture usually does not exhibit "atrophic" changes, and we may assume that the microstructure of its pars tensa remains intact.

With more advanced atelectasis, ie, grades 2 through 4, the atelectatic TM or parts of it lose their usual texture, turning "atrophic." Now they lose their rigidity, becoming flexible, and retract to a deeper level. These atelectatic parts of the TM can be moved easily with the pneumatoscope (with the exception of grade 4), independently of the nonatelectatic parts. Moving an atelectatic part of the TM with a pneumatoscope requires much less pressure than is needed to move the nonatelectatic parts. The specimens examined histologically in this study are examples of atelectasis grades 2 through 4.

The difference in rigidity between the physiologic and the atelectatic TM is probably attributable to the presence or absence of the intact collagenous double layer in the lamina propria of the TM.

Similar to the atelectatic TM, the physiologic Shrapnell's membrane, which is thicker than the pars tensa, also lacks a collagenous "backbone" — the few scattered collagenous fibers present lack any organized architecture[5] — and it is a collapsible membrane.

A similar phenomenon, in the form of a small, circumscribed retraction of the TM, can be seen in the area where a ventilating tube was previously inserted in cases of recurrent secretory otitis media. This dimple occurs in the place where the collagenous layer was traumatized — a spot that now becomes retracted whenever a negative pressure redevelops in the middle ear; for example, when secretory otitis media recurs (Fig 1C).

The pathogenesis of the disruptive process affecting the collagenous layers of atelectatic TMs is probably secondary to an inflammatory process as seen in our present and previous studies.[2] The additional damaging effect of a long-standing negative pressure, even though low, is probably also a contributing factor and should not be underestimated.

Pathophysiologic Aspects of Atelectatic Tympanic Membrane. The relative rigidity of the physiologic TM imparts to the physiologic tympanic cavity the properties of a noncollapsible gas pocket, and considerable pressure is therefore required in order to bring about a change in its shape, ie, to cause it to collapse. In fact, excessive pressure will not change the shape of an inelastic TM; it will cause it to burst. In contrast, collapse — or distention[6] — of an atelectatic part of the TM may be brought about by a relatively small pressure.[7,8] Thus, once the TM or part of it becomes atelectatic and loses its stiffness, the middle ear becomes transformed into a partially collapsible gas pocket.

Middle ear pressure in patients with atelectasis and secretory otitis media, as measured directly by Buckingham and Ferrer[8] and by Sadé et al,[7] is quite less than 100 mm H2O on average. Such a small pressure difference between the TM and the atmospheric pressure may be enough to cause the collapse of a damaged and potentially collapsible atelectatic TM, and probably also of the physiologic Shrapnell's membrane.[9] Such negative pressure is, however, too small a pressure gradient to open the eustachian tube and bring about a flow of air that would equalize the negative middle ear pressure in the atelectatic ear. The pressure gradient required to force open the eustachian tube was measured to be 2 orders of magnitude (up to 400 mm H2O) higher than that existing between atelectatic ears and the atmosphere.[10] Even on swallowing, a minimal pressure difference of 150 mm H2O between the middle ear and the atmosphere is required in order to have gas pass through the tube.[11] Only on rapid ascent or descent, as in flying or diving, do appreciable pressure differences develop between the atmosphere and the middle ear — when pressure differences equilibrate themselves rapidly. It is interesting that under physiologic conditions there hardly exists any pressure gradient between the middle ear and the atmosphere.[12] Under these circumstances the mechanism of air flow into the physiologic middle ear in general, as well as into atelectatic ears in particular, probably requires a more elaborate explanation than is usually conceived.

CONCLUSIONS

This study demonstrates that the mechanical properties of the physiologic pars tensa are probably related to the integrity of its collagenous layer, which is damaged in the atelectatic pars tensa. In an atelectatic TM, such damage will cause the pars tensa to lose its rigidity, thus converting the TM from a noncollapsible to a collapsible membrane. Under these conditions the pars tensa will tend to collapse in the presence of even a slight negative pressure, thereby creating the situation we recognize as an atelectatic condition. The mechanism that can equilibrate pressure differences between the middle ear and the atmosphere is expressed only when large differences exist, as during flight. In atelectatic ears the pressure differences are apparently too small for the eustachian tube to act upon.

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PERIOPERATIVE STROKE IN PATIENTS UNDERGOING HEAD AND NECK SURGERY

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The risk of perioperative strokes has been demonstrated to be very low in general surgical procedures, and somewhat higher in cardiac and carotid artery procedures. We describe 5 patients who underwent major head and neck procedures not requiring carotid ligation and who postoperatively suffered strokes. These occurred between the first and ninth postoperative days. Four of the patients were thought to have had emboli, 3 to the cerebral hemispheres (2 ipsilateral and 1 contralateral to the neck dissections), and another to the lower brain stem. Hypoperfusion was thought to have caused the stroke in the fifth patient. All patients had risk factors for stroke. The cases in our series were difficult to diagnose because of the delayed onset and subtle nature of symptoms, as well as masking of speech and communication due to the operative procedures involved. Thrombogenesis within the internal carotid and vertebral artery systems due to patient positioning and intraoperative cervical manipulation may be an important etiologic factor in this form of stroke.

KEY WORDS — embolism, head and neck surgery, stroke, thrombogenesis.

INTRODUCTION

Perioperative stroke is an uncommon, yet significant, complication of all surgical procedures. The incidence of such events had been reported to be 0.2% in general surgical procedures and as high as 5% in cardiac and carotid artery procedures.[1] Elderly patients undergoing general surgical operations have a slightly higher risk, ranging from 1% to 2.5%.[2] The patient population undergoing head and neck surgery tends to be elderly. Furthermore, patients with head and neck carcinoma frequently manifest medical disorders that place them at risk for stroke, such as diabetes mellitus, hypertension, and organic heart disease.[3]

Surgical excision of head and neck carcinomas often requires complex procedures and prolonged anesthesia time, during which the patient's neck usually remains in extension and is frequently rotated. Many such procedures involve dissection along the carotid artery as well. These factors may increase the risk of perioperative stroke in patients undergoing head and neck surgery. The issue is made more complex by the fact that many such patients are unable to communicate postoperatively because of the nature of the surgical procedure and/or the presence of a tracheotomy, and thus their early symptoms are masked.

Little has been written regarding perioperative stroke in this group of patients. In this communication we report 5 patients who developed strokes in the perioperative period related to major head and neck procedures. We will discuss the nature and possible cause of their strokes, as well as the diagnostic difficulties encountered in the assessment of these patients.

METHODS AND MATERIALS

The medical records of 5 patients at our institution who had undergone major extirpative head and neck surgery complicated by stroke in the perioperative period were reviewed after appropriate clearance by the Institutional Review Board. These cases occurred from 1989 to 1991, during which a total of 105 major extirpative head and neck surgeries were performed. Case histories of the 5 patients are presented below. Of particular interest was the mode of presentation and diagnosis, timing, and probable type of stroke. Patients' prior neurologic, cardiac, and general medical histories, as well as perioperative blood pressure, blood loss, and anesthesia times, were also reviewed for factors that might predispose to stroke.

All of the patients had undergone computed tomography (CT) of the brain after their stroke, reviewed by the neurologic consultant (C.R.G.) to characterize the nature and extent of the stroke.

CASE REPORTS

Patient 1. A 64-year-old man presented with a 4-

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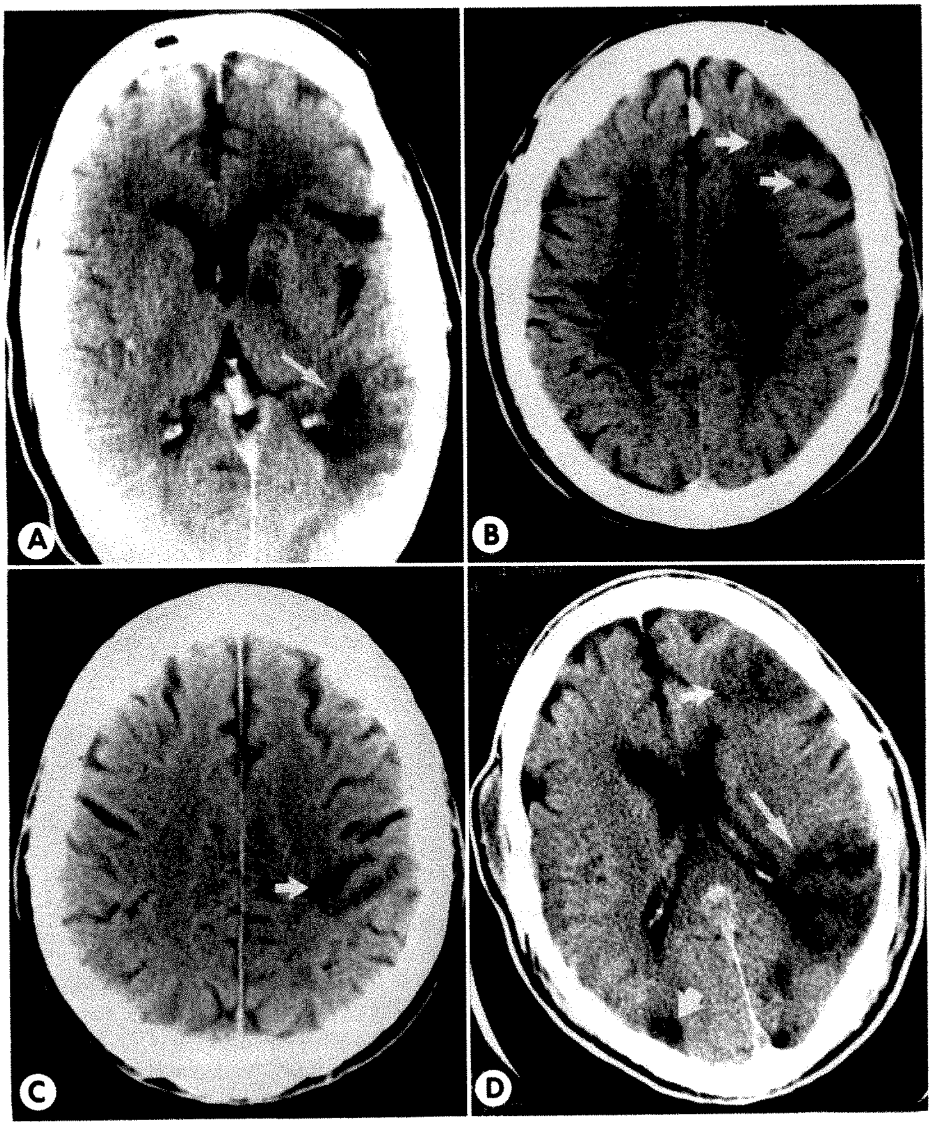

Fig 1. Computed tomograms of brain. A) (Patient 1) Area of hypodensity involving left temporoparietal region (arrow). B) (Patient 2) Infarction of pre–rolandic artery territory (arrows). C) (Patient 4) Infarction of left parietal operculum (arrow). D) (Patient 5) Hypodensities in arterial border zones (arrows).

month history of vocal changes and dysphagia. He had a long history of cigarette smoking and had drunk 4 to 5 beers a day for years. He was judged to have a T4N0M0 squamous cell carcinoma of the larynx after an appropriate evaluation.

His medical history was notable for hypertension and non–insulin-dependent diabetes mellitus.

He was taken to the operating room, where he underwent a tracheotomy, direct laryngoscopy, and esophagoscopy with biopsy, right modified radical neck dissection, and total laryngopharyngectomy with a free jejunal graft reconstruction. His estimated blood loss was 450 mL. During the procedure, 13 hours 15 minutes long, he was normotensive except for a 15-minute period in which his blood pressure was 80 mm Hg systolic and another 15-minute period in which his pressure was 90 mm Hg systolic.

On the first postoperative day, congestion of his flap necessitated a return to the operating room for debridement. The procedure lasted 2 hours 15 minutes, during which his blood pressure never dropped below 100 mm Hg systolic. Estimated blood loss was 160 mL. By postoperative day 2 it was evident that his flap had failed. He was again taken to the operating room for a revision. This procedure lasted 7 hours 15 minutes. His blood pressure remained greater than 100 mm Hg systolic and he lost 400 mL of blood.

Subsequently, the flap remained viable and the patient was transferred to the ward 2 days after his flap revision. He remained stable on the ward until postoperative day 9, when he was noted to be responsive but more lethargic than usual. It was also noted that he was no longer using his communication board appropriately. This pattern of behavior continued into the 10th postoperative day, at which time a neurologic consultation was obtained.

The patient had no motor weakness; however, he would not follow simple commands. He could write smoothly, but without meaningful content; he was unable to copy shapes, letters, or numbers. A CT scan of the brain demonstrated a hypodense lesion in the left cerebral hemisphere involving the temporoparietal region (Fig 1A). The lesion was thought to be consistent with an embolic event involving the inferior division of the middle cerebral artery. A carotid duplex scan demonstrated a 10% to 49% stenosis of the left internal carotid artery. An echocardiogram demonstrated left ventricular apical akinesis, but no thrombus or vegetation were found. A Holter monitor study showed normal findings. No therapeutic intervention was undertaken and by postoperative day 14 the patient was notably more responsive and less lethargic. He was discharged to a rehabilitation unit, where he convalesced but continued to show abnormalities of language comprehension.

Patient 2. A 60-year-old man had undergone a total laryngectomy with subsequent radiotherapy for a T4N0M0 squamous cell carcinoma 11 years prior to presentation. He did well until he developed a left peristomal mass. His evaluation revealed a stomal recurrence of the squamous cell carcinoma. The patient had a 10-pack-year history of cigarette smoking and had drunk 1,200 mL of vodka a day for many years. His medical history was notable for an idiopathic cardiomyopathy with congestive heart failure for which he was taking multiple medications, including warfarin. He was medically cleared prior to surgery and was taken off warfarin 4 days before surgery.

The patient underwent a mediastinal resection of the peristomal squamous cell carcinoma with a left modified radical neck dissection and a pectoralis major myocutaneous flap reconstruction. His estimated blood loss was 500 mL and he received 1 unit of packed red blood cells intraoperatively. His blood pressure did not drop below 100 mm Hg systolic throughout the procedure, 7 hours 45 minutes long.

Postoperatively the patient was closely followed in the intensive care unit by both the otolaryngology and cardiology services. His first 2 postoperative days were unremarkable; however, on postoperative day 3 the patient had a 90-second, right-sided motor seizure. After the seizure, the patient was noted to have weakness of the right side of his body, worse in the upper extremity. A CT scan of the brain demonstrated a small infarction of the left frontal cortex (Fig 1B). The neurologic consultants thought this represented embolic occlusion of 1 of the frontal branches of the middle cerebral artery. The patient was given heparin because of the potential for recurrent cardiogenic brain embolism. Echocardiography at the time showed no evidence of intracardiac thrombus.

Subsequently, the patient progressively improved and by postoperative day 6 he had no residual neurologic deficit. He was transferred to the ward on postoperative day 10 and was ambulating on his own.

Patient 3. A 78-year-old woman had been found to have squamous cell carcinoma of the floor of the mouth 7 years prior to presentation. She had been treated with surgical excision and postoperative radiotherapy. She presented to the otolaryngology service with a large exophytic lesion in the anterior floor of the mouth, later staged as a T4N0M0 squamous cell carcinoma. The patient's medical history was notable for atrial fibrillation, controlled with digoxin, breast cancer treated by mastectomy, and a 40-pack-year history of cigarette smoking. Her preoperative electrocardiogram demonstrated normal sinus rhythm with a primary atrioventricular block.

After medical clearance, the patient was taken to the operating room and underwent an anterior floor of mouth resection, partial glossectomy, bilateral submandibular gland excision, and mandibular symphyseal resection with a trapezius osteomyocutaneous flap reconstruction. The estimated blood loss was 350 mL. Throughout the procedure, 10 hours 15 minutes, the patient's blood pressure never dropped below 100 mm Hg systolic.

Two days postoperatively, the patient was noted to be unresponsive to verbal stimuli. A neurologic consultation noted that the patient had reactive pupils and was able to move her eyes; however, she did not move any of her limbs. This finding was believed to be consistent with a locked-in syndrome, and indicative of brain stem ischemia. A CT scan failed to document any brain lesions. Two days later, however, the patient spontaneously became responsive to commands and moved all 4 extremities. She was transferred to the floor on postoperative day 6 and by the ninth postoperative day had only some residual right lower extremity weakness and was able to ambulate with a walker.

Patient 4. A 65-year-old man presented to the otolaryngology service with a left-sided neck mass of 7 weeks' duration. Fine-needle biopsy of the mass demonstrated squamous cell carcinoma. A CT scan of the head and neck and prior panendoscopy at an outside institution had failed to find the primary lesion. The lesion was staged TxN2aM0. The patient's medical history was notable for non–insulin-dependent diabetes mellitus, hypertension, and peptic ulcer disease, although he denied these problems preoperatively. He was taking no medications at the time of surgery. He had smoked 5 cigars per day for 35 years and characterized himself as an occasional alcohol user.

PATIENT CASE HISTORIES AND STROKE CHARACTERISTICS

Pt	*Age (y)*	*Sex*	*Tumor and Stage*	*Procedure*	*Stroke Risk Factors*	*Infarction Territory*	*Proposed Mechanism*	*CT Documentation*
1	64	M	SCCA larynx, T4N0M0	Tracheotomy, panendoscopy, right MRND, total laryngopharyngectomy with FJG, FJG revision x2	Hypertension, NIDDM, smoking	Left inferior middle cerebral artery division	Embolic	Fig 1A
2	60	M	SCCA peristomal recurrence	Mediastinal resection, left MRND, pectoralis major myocutaneous flap	Idiopathic cardiomyopathy, congestive heart failure, smoking	Left frontal middle cerebral artery branch	Embolic	Fig 1B
3	78	F	SCCA floor of mouth, T4N0M0	Floor of mouth resection, partial glossectomy, bilateral submandibular gland excision, mandibular resection with trapezius osteomyocutaneous flap	Atrial fibrillation (controlled), smoking	Vertebrobasilar (penetrating branches)	Uncertain (embolic?)	No CT
4	65	M	SCCA left tongue base, T1N2aM0	Panendoscopy, partial glossectomy, left MRND	Hypertension, NIDDM, smoking	Left parietal middle cerebral artery branch	Embolic	Fig 1C
5	62	M	SCCA recurrence in persistent left pharyngocutaneous fistula	Excision of fistula with latissimus dorsi myocutaneous flap reconstruction	Smoking	Left arterial border zones	Hypotension	Fig 1D

CT — computed tomography, SCCA — squamous cell carcinoma, MRND — modified radical neck dissection, FJG — free jejunal graft, NIDDM — non-insulin-dependent diabetes mellitus.

The patient was taken to the operating room and underwent a direct laryngoscopy with base of tongue biopsies that demonstrated a T1N2aM0 squamous cell carcinoma on the left side of the base of the tongue. He also underwent an esophagoscopy and a left modified radical neck dissection. His estimated blood loss was 400 mL. His blood pressure was noted to be 80 mm Hg systolic for 25 minutes and 100 mm Hg systolic for 1 hour 45 minutes of his procedure, which was 6 hours 15 minutes long.

The patient was noted to be mildly lethargic on the first postoperative day. The lethargy was attributed to recent anesthesia and analgesia; he was otherwise stable and was transferred to the floor. In spite of minimized analgesia, he remained slightly lethargic the next day, and on postoperative day 3 he was noted to have difficulty with fine motor skills and coordinated motion of the right upper extremity. A neurology consultation noted that the patient had a fluent aphasia with some weakness and motor apraxia of the right upper extremity, consistent with a left cerebral infarct. A CT scan of the brain demonstrated a left cerebral infarct of the parietal operculum with dolichoectasia of the middle cerebral arteries bilaterally (Fig 1C). The lesion was thought to represent embolic occlusion of a cortical branch of the middle cerebral artery. A carotid duplex scan did not demonstrate any hemodynamically significant lesions. Echocardiography demonstrated neither thrombus nor vegetation.

No specific therapeutic intervention was considered necessary. The patient began occupational therapy on postoperative day 5 with decreased symptoms, and by the sixth postoperative day he had marked improvement. He is currently without neurologic deficit.

Patient 5. A 62-year-old man had undergone total laryngectomy, left tongue-jaw-neck resection, and subsequent left pectoralis major and trapezius myocutaneous flap reconstructions for recurrent squamous cell carcinoma. After resection of his recurrence, he developed a persistent left pharyngocutaneous fistula that did not resolve with conservative treatment. He had an 80-pack-year cigarette smoking history and a heavy beer-drinking history.

His medical history was otherwise unremarkable. He was taken to the operating room for a left latissimus dorsi myocutaneous flap reconstruction of the pharynx. The estimated blood loss was 1,000 mL, and he received 4 units of packed red blood cells during his 8-hour operation. During the procedure, his systolic blood pressure dropped to 85 mm Hg and remained at similar levels for a total of 45 minutes. Systolic blood pressures of 60, 70, 75, and 80 mm Hg were recorded for periods of 5 minutes each.

On the first postoperative day, the patient was noted to be unarousable and unresponsive to painful stimuli; wandering eye movements were observed. A neurologic consultation was obtained. The patient opened his eyes to voice, but did not follow verbal commands. His pupils were slowly reactive. He showed bilateral hyperreflexia, more prominent on the right side. His plantar reflexes were extensor bilaterally. A CT scan demonstrated bilateral arterial border-zone infarctions, larger on the left side (Fig 1D).

The patient's condition remained unchanged until the fourth postoperative day, when he demonstrated gross responses to verbal commands. His neurologic findings remained unchanged from that time. He was transferred to the ward on postoperative day 11, and his hospitalization was subsequently complicated by an aspiration pneumonia and the development of a peristomal recurrence of his tumor. He was discharged to a rehabilitation center on postoperative day 24.

RESULTS

The characteristics of the patients' cerebrovascular events are summarized in the Table. Four of the 5 patients were men, and the average patient age was 65.8 years. None had a history of stroke or transient ischemic attack. Two of the 5 patients had a preoperative history of heart disease. All patients in the study had medical risk factors for stroke.

During the 2 years in which these strokes occurred, there were a total of 105 major extirpative head and neck operations performed. Thus, the incidence of stroke in this series was 4.8% during the study period.

Intraoperative hypotension (defined as a greater than 10-minute period of systolic blood pressure less than 80 mm Hg[1]) occurred in 1 patient; this was an intraoperative event. The average blood loss was 652 mL, and the average procedure duration was 8 hours.

Of the 5 strokes, 3 were thought to have involved cerebral emboli, 2 of which were ipsilateral and 1 of which was contralateral to neck dissection. The fourth patient had a low brain stem infarct. The fifth stroke was considered to be due to hypoperfusion. The strokes occurred an average of 3.2 days postoperatively.

DISCUSSION

The term stroke encompasses all acute neurologic events caused by a sudden derangement of the cerebral circulation. More specifically, ischemic stroke is that which results from insufficient delivery of blood and substrates to an area of the brain. It is this type of stroke that was suffered by our patients. Stroke is crudely associated with sudden or at least rapid development of signs and symptoms. Multiple risk factors have been associated with stroke. Among these, hypertension, diabetes mellitus, heart disease, smoking, and prior transient ischemic attacks or strokes account for the greatest impact in the production of stroke. Alcoholism and hypercoagulative states have also been suggested to increase the risk of stroke.[3]

Perioperative stroke is an unusual event, with incidences reported to be 0.2% to 2.5% in general surgical cases[1,2] and up to 5% in cardiac and carotid artery procedures.[1] Even in patients with a history of stroke, the risk remains low, and has been reported at 2.9%.[4] Interestingly, in this series, the incidence of stroke was 4.8%, a figure that most likely reflects the more elderly age of our patient population, as well as the frequency and necessity of cervical and arterial manipulation.

Of the perioperative strokes that are known to occur, greater than 80% of them do so in the postoperative period,[2] at a mean of 10 days after the operation.[1] In general, they have been most frequently said to be the result of embolic mechanisms.[2] Other mechanisms of perioperative stroke have been suggested to include hypotension (intraoperative or postoperative) and hypercoagulability,[2] with risk factors similar to those for general stroke: old age, cardiac disease, previous stroke, hypertension, and peripheral vascular disease.[1] The presence of bruits or carotid artery stenosis based on noninvasive testing has not been predictive for the occurrence of perioperative stroke.[2]

Patients who present with head and neck malignancies are frequently elderly and in poor medical condition; furthermore, they often smoke and consume alcoholic beverages. It is notable that all patients reported had medical risk factors for stroke, and that in particular, 40% of them had heart disease. The general health status of this population would seem to increase the risk for perioperative stroke compared to the population undergoing general surgery as a whole.

Strokes in this series occurred an average of 3.2 days postoperatively. In patients 2, 3, and 5, diagnosis of stroke was not difficult because of gross neurologic deficits. However, the presentation of patients 1 and 4 was quite subtle. Their findings were originally believed to be the result of postoperative anesthetic and analgesic effects, and it was only after some time had elapsed that neurologic consultation was considered necessary. These 2 cases demonstrate the potential difficulty in diagnosing perioperative stroke in patients who have undergone major head and neck surgery.

In particular, this difficulty results from the fact that many such patients have undergone tracheotomy or extirpative procedures involving the oral cavity, and thus are unable to express neurologic

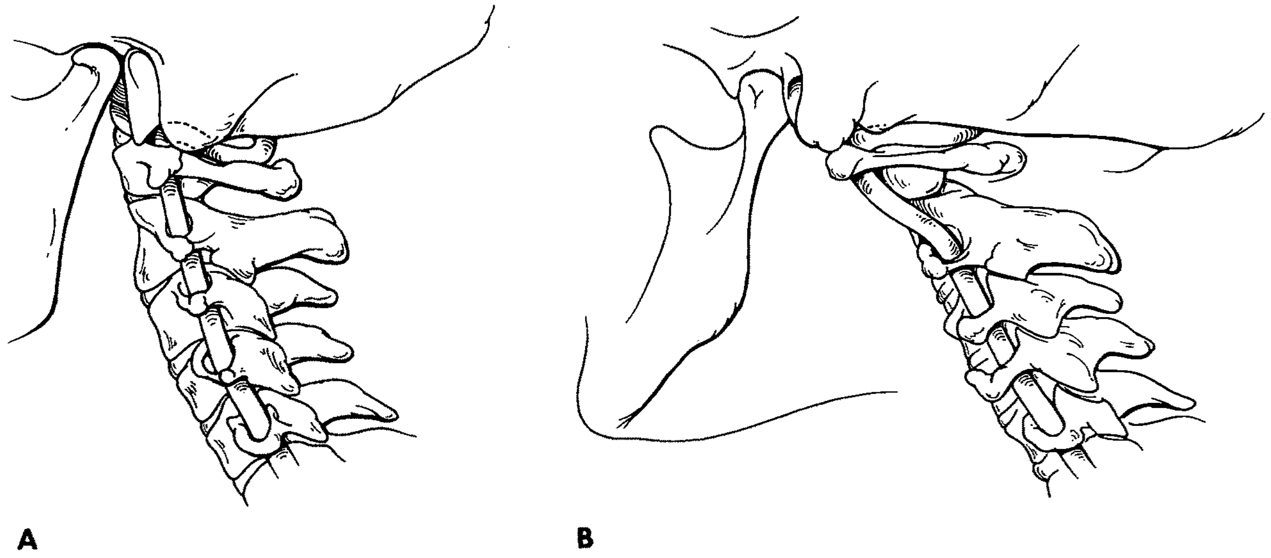

Fig 2. Demonstration of A) course of vertebral artery at atlantoaxial level and B) effect of contralateral rotation.

complaints or easily display signs of aphasia. The very nature of their surgery may therefore mask a potentially severe complication.

One of these 5 strokes appeared to be due to intraoperative hypotension, 2 were secondary to embolism, presumably originating in the carotid artery, 1 was due to cardiogenic embolism, and the fifth was of uncertain cause. The last, however, may have been due to cardioembolism, since the patient suffered from atrial fibrillation, but this is not confirmed.

Consideration of the stroke mechanism in the patients who had presumed embolism requires a brief review of the anatomy of the vertebral and carotid arteries in the cervical region. The vertebral arteries enter the foramen of the transverse process of the sixth cervical vertebra and course through the vertebral canal until exiting the atlas (C-1).[5,6] They then turn posteriorly around the superior articular process of C-1 and then medially, penetrating the atlanto-occipital ligament as they pass through the foramen magnum (Fig 2A).[6] Blood flow through the vertebral arteries has been demonstrated to decrease during extension and rotation of the neck.[7] Furthermore, rotation of the head at the atlantoaxial level is thought to cause stretching and compression of the vertebral arteries (Fig 2B) that may lead to intimal tear, thrombus formation, or vascular occlusion due to vasospasm, any of which are capable of causing embolism into the basilar artery system.[6,8] Such damage has been confirmed radiographically and in autopsy specimens.[6] There have been numerous reports of brain stem stroke following passive and active cervical manipulation.[6-12]

The internal carotid artery courses superiorly in the carotid sheath. At the level of the atlas, the carotid artery is immediately anterior to the transverse process of C-1 (Fig 3A).[7,8,13,14] Shortly thereafter, the internal carotid artery enters the carotid canal at the skull base, at which point it is attached.[14,15] Hyperextension of the neck has been suggested to stretch the artery and, with simultaneous rotation of the neck, is thought to cause contralateral arterial impingement due to compression from the lateral process of the atlas (Fig 3B). This dynamic relationship has been demonstrated to cause intimal tears, which can act as a nidus for thrombus and possible embolus formation.[8,13-15] Cadaver studies have shown flow reduction with head extension and rotation, although most commonly ipsilateral to rotation.[7]

Most major head and neck procedures require the patient to maintain the neck in an extended and rotated position for a prolonged period of time; others require frequent rotation of the neck for optimal exposure. Our patient 3 required extensive dissection of the floor of the mouth, bilateral submandibular gland excision, and trapezius osteomyocutaneous flap reconstruction. This patient subsequently developed a low brain stem infarct. It is highly likely that during this procedure the patient's head was rotated many times, and it is also possible that intimal damage occurred within the vertebral artery system, which, particularly in a low flow state, could have led to thrombus with subsequent embolus formation.

Patients 1, 2, and 4 underwent procedures involving neck dissection. Their subsequent strokes seemed embolic and, in 2 of the 3 cases, were ipsilateral to the neck dissection. In patient 1, the cerebral lesion was contralateral to the neck dissection, and subsequent studies demonstrated that the internal carotid artery

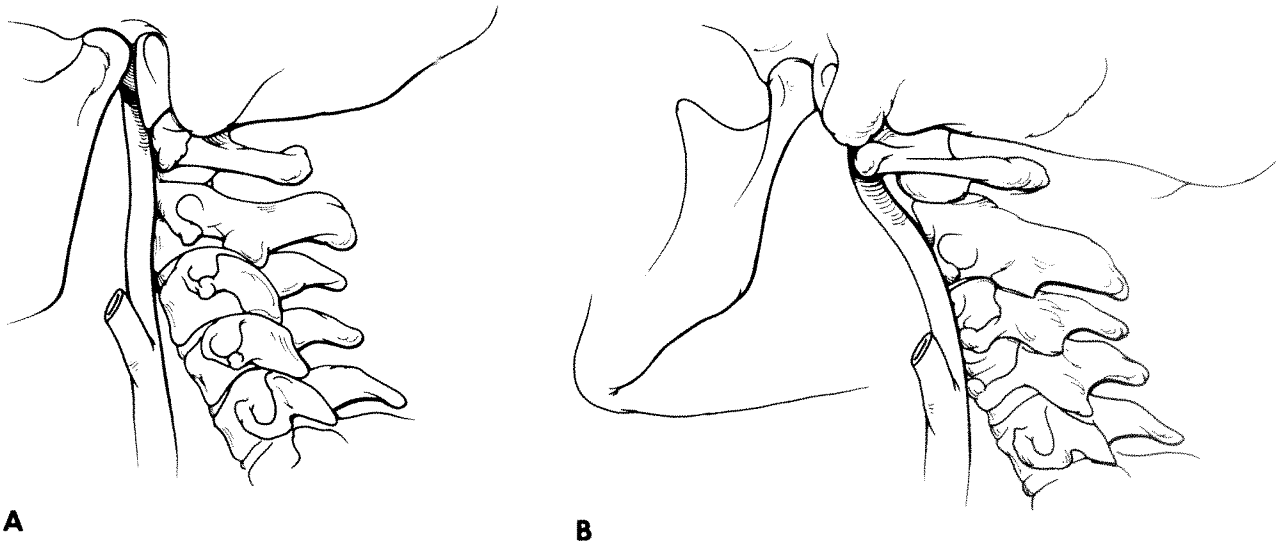

Fig 3. Demonstration of A) course of internal carotid artery at level of atlas and B) effect of hyperextension and contralateral rotation.

on the side of the stroke had a 10% to 49% stenotic segment. It is quite possible that this lesion, in combination with a possible low flow state, may have allowed thrombus formation and subsequent embolism.[7] In patients 2 and 4, the strokes were ipsilateral to the side of neck dissection. In these cases the neck was extended and rotated away from the side of the stroke throughout the dissection. Subsequent carotid duplex studies did not show stenosis in either patient. It is possible that internal carotid impingement, stretch intimal injury, and possible low flow state may have caused transient thrombus formation and ultimate embolization.

Although uncommon, perioperative stroke may occur in patients undergoing head and neck surgery. In this series, all patients had medical risk factors for stroke. Presentation was often subtle, and head and neck surgeons must have a high index of suspicion, since communication is often difficult for such patients. Carotid and vertebral artery thrombogenesis due to cervical manipulation may play a role in stroke causation; meticulous surgical technique and careful intraoperative positioning may be helpful in minimizing this complication. Further delineation of stroke etiopathogenesis in this population, however, is still necessary.

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PERSISTENT STAPEDIAL ARTERY: DOES IT PREVENT SUCCESSFUL SURGERY?

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Because of the important function of the embryologic stapedial artery, it is taken for granted by many surgeons that the finding of such a persistent artery in postnatal humans during middle ear surgery should urge maximal caution in order not to damage the artery. Often, discontinuation of the surgery is recommended. Yet this attitude is based on theoretic considerations rather than on any clinical evidence of complications following injury to this vessel. The present paper describes the embryology in relation to this specific aspect and reviews the literature on the persistent stapedial artery, emphasizing the papers dealing with injury to this vessel. In addition, we report 4 cases of persistent stapedial artery from the files of almost 20,000 patients in whom tympanotomy was performed. From all these data we conclude that injury to this artery or even complete section probably does not cause major, if any, postoperative sequelae, and that consequently, middle ear surgery is not necessarily hindered by the presence of this vessel.

KEY WORDS — congenital hearing loss, facial nerve, middle ear, stapedial artery, stapes surgery.

INTRODUCTION

Embryologically, the stapedial artery is a very important blood vessel. In humans the stem disappears at about 10 weeks of age, and the blood supply of the distal divisions is taken over by the external carotid artery.[1] However, a persistent stapedial artery is sometimes encountered during middle ear surgery or during postmortem examination. On the basis of its theoretic area of blood supply, injury to this artery is considered to be fairly hazardous, and many surgeons have advocated interrupting a surgical intervention when a persistent stapedial artery is found. But this policy is not supported by any clinical evidence. On the contrary, the few reports that mentioned injury or section of this artery did not observe any postoperative complications. The present paper reports on 4 more patients with a persistent stapedial artery, 2 of whom underwent elaborate middle ear surgery.

Embryology. The dorsal end of the second aortic arch, which originates from the internal carotid artery, constitutes the hyoid artery, a remnant of which is the caroticotympanic artery in adults.[2] The hyoid artery serves as the stem of the stapedial artery. A small posterior branch of the stapedial artery supplies the posterior tympanic cavity, the stapedial muscle, and the mastoid. The main stem of the stapedial artery splits into an upper and a lower branch. The anterior or supraorbital division of the upper branch gives rise to the supraorbital, frontal, anterior ethmoidal, and lacrimal arteries. The posterior division of the upper branch gives rise to meningeal and temporal rami and to the arteria diploëtica magna. The lower (or maxillomandibular) division gives rise to the inferior alveolar and the infraorbital arteries.[2-4] At this stage, as at the adult stage in some primitive eutherians, the stapedial artery forms the primary blood supply to the nonneural tissues of the head.[5] The stapedial anlage at its earliest stage of development is a solid blastema lacking an oburator foramen.[6] In the 6-week-old embryo, this anlage folds around the stapedial artery, thus forming a dense mesenchymal ring with an obturator foramen.[7] At 9 weeks the stapes is cartilaginous.[7] Beyond a certain body size, the stapedial artery can no longer function as the sole supplier of its original territory, because the diameter of its stem is limited by the size of the intercrural foramen of the stapes.[5] Hence, the distal portion of the ventral pharyngeal artery — which is the precursor of the external carotid artery, directly arising from the aortic sac — joins with the maxillomandibular division of the stapedial artery. Subsequently, at 10 weeks of age, the stem of the stapedial artery atrophies and the anastomosis with the external carotid artery takes over the blood supply of both the upper and lower branches of the former stapedial artery.[1,8]

PATIENTS AND METHODS

Two cases of persistent stapedial artery were re-

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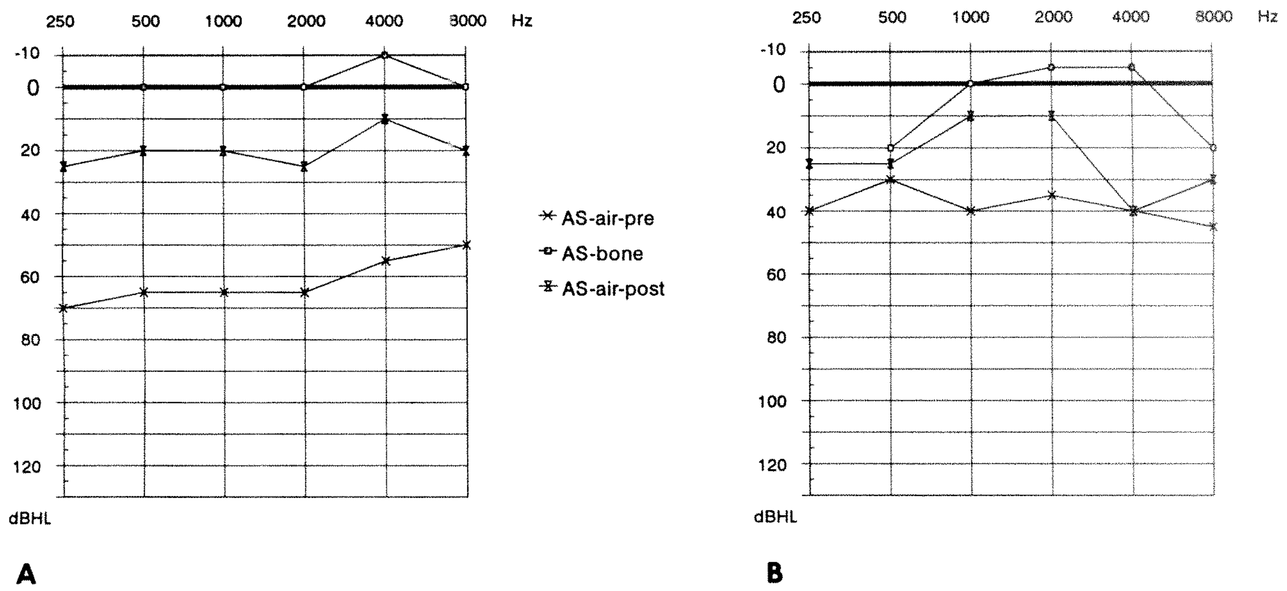

Fig 1. Audiograms of left ears (AS) showing preoperative and postoperative results. A) Case 2. B) Case 3.

trieved from the files of the University Hospital Nijmegen, and another 2 cases from the private files of one of the authors (F.E.O.) and of the late Prof Dr J. Marquet (St Augustinus Medical Institute, University of Antwerp). The files of the latter should have contained yet another case, as reported previously,[9] but the authors were not able to locate it. On the basis of the number of middle ear operations in the two groups, the prevalence of the anomaly can roughly be estimated at 2 in 7,500 and 3 in 12,000, respectively. This lies in the same range as the 1 in 5,000 to 1 in 10,000 prevalence reported by Schuknecht.[10] The first case belongs to the well-documented Nijmegen group of 144 ears with a congenital minor ear anomaly that underwent tympanotomy.[11] The second case from Nijmegen was encountered more recently and was therefore not included in this selected group of 144 cases. These data show that the prevalence of this anomaly in a selected group of congenital minor ear anomalies with conductive hearing loss is approximately 1 in 150.

RESULTS

Case 1. A 4-year-old boy was referred to the otolaryngology department (Nijmegen) with a bilateral conductive hearing loss of 70 dB.[12] Exploratory tympanotomy of the left ear revealed several middle ear malformations. The chorda tympani was located too high in the epitympanum, the round window was situated in the center of the promontory, the facial nerve was not covered by bone, the long process of the incus was broad and connected to rudimentary stapedial crura, and there was no stapedial muscle or stapedial footplate. Surgery was discontinued. The right ear was operated on at the age of 14 years (Nijmegen). The facial nerve was not covered by bone. The stapedial crura were rudimentary and a stapedial footplate was lacking. A pulsating artery was observed that ran from the round window between the rudimentary stapedial crura to enter the facial canal. The intervention was discontinued.

Case 2. A 14-year-old girl underwent exploratory tympanotomy on her left ear for alleged congenital conductive hearing loss (Nijmegen). The preoperative audiogram showed conductive hearing loss with a Fletcher index (mean of thresholds at 500, 1,000, and 2,000 Hz) of 65 dB (Fig 1A). Middle ear inspection revealed stapedial ankylosis. A persistent stapedial artery was found running through the obturator foramen of the stapes (Fig 2A). A calibrated hole was drilled posteriorly in the stapes footplate. Both crura of the stapes were fractured. During fracturing of the anterior stapedial crus with stapedial crural scissors, the artery was injured and profuse bleeding ensued. After the bleeding was stopped with Tabotamp (Johnson & Johnson), a Teflon-wire prosthesis was placed (Fig 2B) and the Tabotamp was removed. No postoperative complications occurred. The audiogram showed a Fletcher index of 20 dB (Fig 1A).

Case 3. An 8-year-old girl underwent middle ear surgery on her left ear for chronic otitis media with cholesteatoma (Antwerp). The preoperative audiogram showed conductive hearing loss with a Fletcher index of 35 dB (Fig 1B). Mastoidectomy, antroatticotomy, and posterior tympanotomy were performed. The long process of the incus and the posterior crus of the stapes had been destroyed. The incus was removed together with the entire cholesteatoma. A large stapedial artery was also present. Careful dissection of the cholesteatoma did not injure the artery.

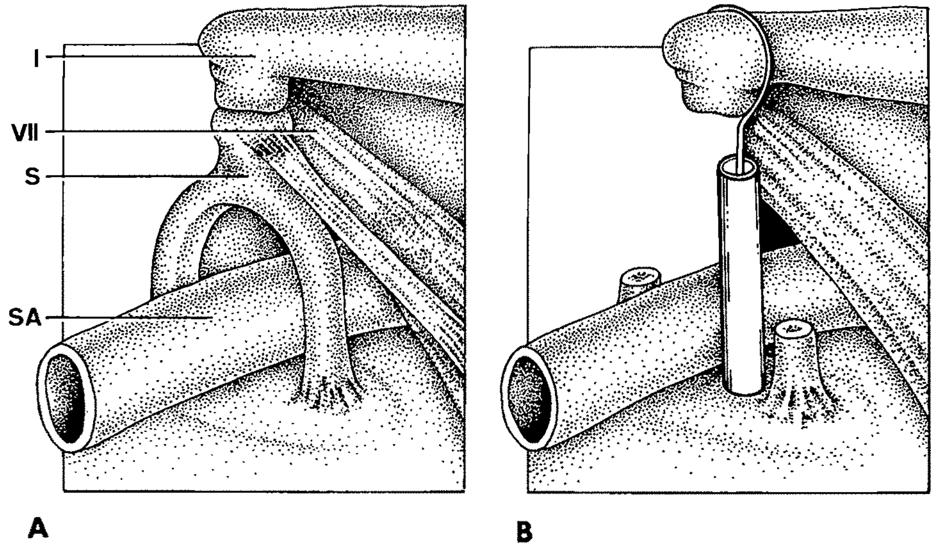

Fig 2. (Case 2) Schematic representation of perioperative findings. A) Persistent stapedial artery (SA). I — incus, VII — facial nerve, S — stapes. B) Teflon-wire prosthesis in calibrated hole in posterior part of footplate.

A monoblock tympano-ossicular allograft (tympanic membrane, malleus, and incus) was implanted.[13] No postoperative complications occurred. The audiogram showed a Fletcher index of 15 dB (Fig 1B). During a second-look operation 1 year later, the middle ear and mastoid were free of residual cholesteatoma.

Case 4. A 20-year-old woman underwent tympanotomy on her left ear and 2 years later on her right ear for mixed hearing loss with preoperative Fletcher indices of 65 dB (right ear) and 70 dB (left ear; Antwerp). A persistent stapedial artery was found on both sides. The right facial nerve was prolapsed against the stapes, and there was no stapedial muscle. Both stapes footplates showed ankylosis and were mobilized during an attempt to fracture the crura. In consequence the ears were closed. The postoperative Fletcher indices were 45 dB (right ear) and 70 dB (left ear).

DISCUSSION

The stapedial artery persists completely in quite a number of animals and partially in others. It is persistent in rodents, and in the guinea pig it passes between the crura of the stapes.[14] A persistent stapedial artery is rare in humans. The first report was published by Hyrtl[15] in 1836. House and Patterson[16] reviewed 17 reported cases in 1964. We were able to review 27 additional reported cases and add 4 cases from our own files,[2,3,8,12,14,17-32] making a total of 48 cases. Most of the data concern incidental findings during postmortem examination or during middle ear (mostly stapes) surgery. A prevalence of about 1 in 5,000 to 1 in 10,000 is estimated.[10] In merely 12 cases (including the present cases 2 and 3) this was an isolated finding, while the other cases showed multiple congenital anomalies (see Table[2,8,14,16,18,19,23,24,27-29,32-37]). Ten cases, including the present case 4, had documented bilateral stapedial arteries. Twelve cases, including the present cases 2 and 4, showed stapedial footplate ankylosis. Eleven cases, including the present case 2, underwent stapedotomy, and in 9 cases, including the present case 2, a stapedial prosthesis was implanted. The artery was injured, clipped, or sectioned in 7 cases, including the present case 2.

The course of the persistent stapedial artery has already been described in detail in other papers.[2,8] The artery enters the middle ear cavity in the anterior inferior quadrant, then crosses the promontory just lateral to the round window membrane to course backward and upward, where it passes through the obturator foramen of the stapes, close to the anterior crus. It then immediately enters the horizontal portion of the facial canal through a bony dehiscence, usually located behind the cochleariform process. It leaves the facial canal, usually superiorly, dividing into an intracranial dural branch, substituting for the middle meningeal artery and a sphenoidal branch, anastomosing by a small branch to the orbital vessels. On the basis of the embryologic evolution of this vascular system, a persistent stapedial artery could hypothetically be of serious clinical importance by supplying part of the pyramidal tract in the region of the geniculate ganglion, as well as part of the medial lemniscus and of the trapezoid body. Hogg et al[1] warned of possible clinical implications of sectioning a persistent stapedial artery, such as transient or permanent crossed hemiplegia, tabes dorsalis–like symptoms, or hearing loss. Finding such a stapedial artery during middle ear surgery caused great concern for the surgeon to avoid injuring it and was often considered a reason to discontinue the operation. "A persistent stapedial artery should be treated with respect when found."[38(p1241)] Only 11 cases (including the present case 2) are described of stapedectomy

REVIEW OF LITERATURE ON PERSISTENT STAPEDIAL ARTERY

Authors	*PSA in 1 or 2 Ears*	*Footplate Ankylosis*	*Stapes Surgery*	*Stapes Prosthesis*	*Postop AB Gap*	*Injury to PSA*
Postmortem examination, other congenital anomalies present						
Altmann[33]	2	NA	–	–	NR	NR
Kelemen[34]	2	NA	–	–	NR	NR
Sando et al[19]	2	NA	–	–	NR	NR
Egami et al[23]	2	NA	–	–	NR	NR
Harada and Sando[27]	2	NA	–	–	NR	NR
	2	NA	–	–	NR	NR
	2	NA	–	–	NR	NR
In vivo examination, other congenital anomalies present						
De Pinnies and Ongsiaka[37]	1*	–	–	–	NR	Bleeding
Maran[14]	1	+	+	+	80	–
Marion et al[8]	2	NA	–	–	NR	NR
Our case 1	1	–	–	–	60	–
Our case 4	2	+	–	–	45-70	–
In vivo examination, no other congenital anomalies						
Hough[35]	2	+	+	–	Excellent	Bleeding
Baron[36]	1*	+	+	+	0	–
House and Patterson[16]	1*	+	+	+	Closure	–
	1*	+	+	+	Closure	–
Steffen[2]	1	+	+	NA	NA	NA
Gerhardt and Otto[18]	1*	+	+	+	5	Cut
Schweitzer and Lilly[28]	1*	+	+	+	0	Cut
Fisch et al[24]	1*	–	–	–	NR	Clip
Yamamoto and Hirono[29]	1	+	+	+	5	Cut
Pahor and Hussain[32]	1	+	+	+	5	–
Our case 2	1*	+	+	+	20	Bleeding
Our case 3	1*	–	–	–	15	–

PSA — persistent stapedial artery, AB — air-bone, NA — not available, NR — not relevant.

*No information available on second ear.

in an ear with a persistent stapedial artery, and only 1 patient had elaborate middle ear surgery for cholesteatoma (the present case 3). As shown in the Table, functional results are very good and comparable to ordinary stapedotomy results if the persistent stapedial artery is an isolated anomaly. On the contrary, in cases of associated congenital abnormalities (see Table), the functional results appear to be rather poor. The mere presence of the artery, however, does not seem to impair the functional results. Three authors mentioned having injured this artery, and 4 mentioned having cut or clipped the vessel without any postoperative complications (see Table). To our knowledge no cases of damage to the artery have led to unfavorable results. It is possible to cautiously interpret these data to mean that a persistent stapedial artery in the postnatal human no longer forms the main blood supply to any important structure in the head. Probably, sufficient collaterals exist to provide an alternative blood supply.

In conclusion, the finding of a persistent stapedial artery during middle ear surgery should not impede the intervention. Stapes surgery may be equally as successful as it would have been without this vessel. Injury to this artery is not likely to have any consequences but bleeding, which can adequately be dealt with. The present paper gives evidence that successful middle ear surgery, both functionally and anatomically, is highly practicable.

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TRAUMATIC MACROGLOSSIA

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A case of severe macroglossia resulting from trauma (tongue biting) during eclampsia and causing respiratory obstruction is described. Despite medical treatment with steroids and antibiotics for a week, followed by tracheostomy, no significant improvement was observed. After an energetic but cautious maneuver of reducing and restraining the tongue in the oral cavity, the swelling reduced dramatically in 24 to 48 hours. Earlier manual replacement of the tongue into the oral cavity is advised in order to arrest the cycle of venous and lymphatic obstruction and congestion that leads to further edema and increased tongue swelling. The mechanism of traumatic macroglossia is discussed.

KEY WORDS — macroglossia, respiratory obstruction, trauma.

INTRODUCTION

Macroglossia is relatively uncommon. Most clinicians see an occasional case in the course of their practice. Review of the literature shows several case reports of congenital macroglossia, in which lymphangioma, hemangioma, neurofibroma, and macroglossia of Down syndrome are described. Macroglossia from these causes is slow-growing and rarely causes airway obstruction.

Traumatic macroglossia is rarely reported. It is significant because of the rapidity with which tongue enlargement occurs and the airway obstruction it may cause.

In this presentation we describe an unusual and interesting case of traumatic macroglossia and its management.

CASE REPORT

A 33-year-old woman, 5 hours post–vaginal delivery, had eclamptic seizures and bit her tongue. She developed a huge tongue hematoma and respiratory distress, and was intubated with difficulty and transferred to the respiratory care unit. She was treated expectantly with steroids and antibiotics, but the tongue hematoma progressed (Fig 1).

On day 7 an otolaryngology consultation was requested. A tracheostomy was done for fear that if she extubated herself accidentally reintubation would be very difficult.

By days 8 and 9 the tongue swelling had continued to increase. On day 9 the patient was taken to the operating room, and under general anesthesia the huge tongue was massaged into the oral cavity and

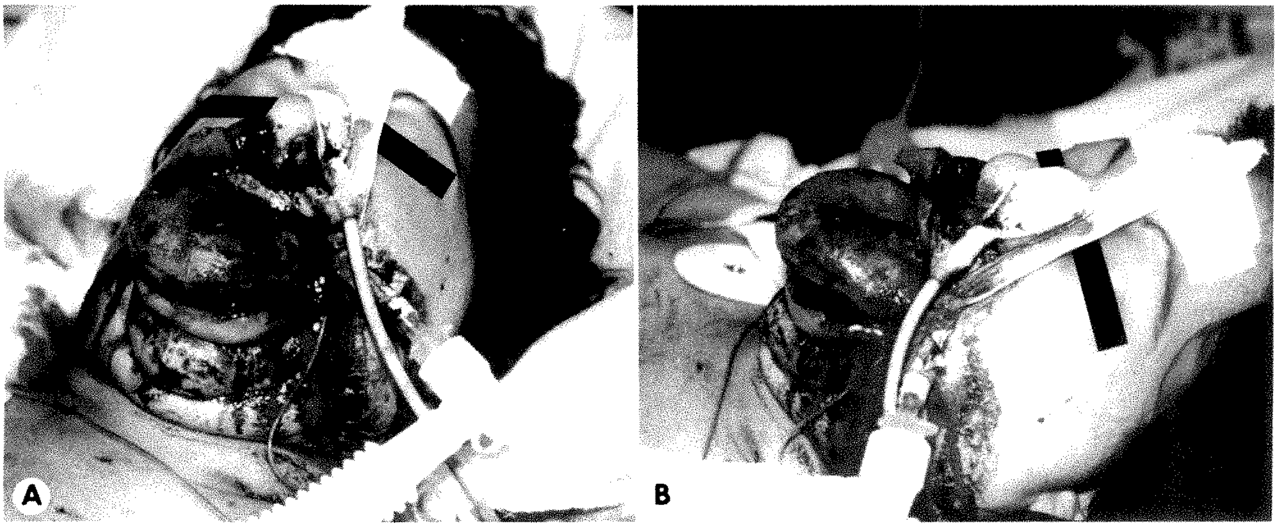

Fig 1. Massive macroglossia with hemorrhage, edema, and mucosal pallor. A) Front view. B) Lateral view.

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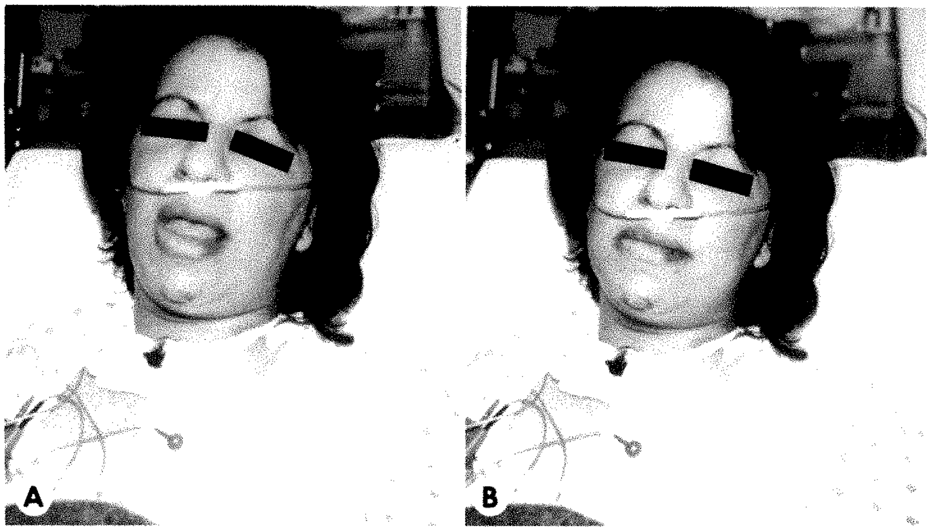

Fig 2. Same patient following tongue massage and reduction. A) Mouth open. B) Mouth closed.

restrained by strapping the jaws together with a gauze bandage.

The tongue edema had reduced considerably 24 to 48 hours later (Fig 2). The patient was subsequently decannulated and discharged home.

DISCUSSION

Macroglossia is defined as a resting tongue that protrudes beyond the teeth or alveolar ridge.[1] Vogel et al[2] developed a clinical classification for defining true and relative macroglossia and subdivided these into congenital and acquired types. The anatomic features of the tongue — its superficial vascular supply — when subjected to trauma make apparent the potential for venous and lymphatic obstruction. However, macroglossia of traumatic origin is rare, and only a few cases have been reported. Kurlemann et al[3] in their case report described a 17-year-old patient in hypertensive crisis who had seizures and bit his tongue. Hemorrhage into the tongue caused macroglossia with respiratory obstruction necessitating a tracheostomy. The macroglossia resolved in 6 days. Tongue biting, usually seen in seizure episodes or maxillofacial trauma, causes soft tissue, vascular, and lymphatic injury. Hemorrhage and hematoma formation cause tongue swelling and increased mass.

Our patient had several seizure episodes with bites on the tongue causing soft tissue, vascular, and lymphatic injury. Hemorrhage and hematoma formation caused enormous tongue swelling. The tongue protruded from the oral cavity and was strangulated between the teeth. The teeth's pinching the tongue created more edema, making the tongue even more swollen. A vicious cycle was thereby created. Active mobilization of the huge tongue into the oral cavity and restraining it there helped to improve the patient's condition.

The advantages of this maneuver are twofold. First, the tongue swelling reduces much more quickly than when the tongue is left alone, and thus morbidity is decreased. Second, replacing the tongue into the oral cavity prevents drying, fissuring, and superficial infection and more swelling.

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IMAGING CASE STUDY OF THE MONTH

METASTATIC TONSIL MELANOMA

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INTRODUCTION

Head and neck mucosal metastasis of malignant cutaneous melanoma is extremely rare. Since 1912, fewer than 100 cases have been reported in the English-language literature.[1-16] Involvement of the tonsil was noted in about one fourth of the cases.[5,8,10,11,14,16] A case of tonsil metastasis from a malignant cutaneous melanoma is presented. A review of the literature is presented.

CASE REPORT

A 41-year-old man presenting with a right subdigastric lymph node of 2 months' duration was referred to our institution. Physical examination revealed an enlarged, slightly painful right tonsil. The overlying mucosa was normal in appearance, without any ulceration. The underlying mass was lobulated and firm when palpated. The remainder of the findings on head and neck examination were unremarkable.

His medical history revealed removal of a cutaneous malignant melanoma from the right thigh, at another institution, 6 years earlier. The tumor was stage IV according to the staging system of Clark et al.[17] The margins of resection were free of tumor. An ipsilateral inguinal lymph node dissection was performed 18 months later because of regional lymph node recurrence. Multiple inguinal nodes were involved, and extracapsular spread was noted in 1 of them. Postoperative radiotherapy to the thigh and the inguinal region delivered 45 Gy. Following radiotherapy, 2 courses of chemotherapy with a 1-month hiatus were performed. Bleomycin sulfate (15 mg on days 1 and 4), vindesine sulfate (Vindesine, 3 mg/m^2 on days 1 and 5), and dacarbazine (Deticene, 200 mg/m^2 from day 1 through day 5) were delivered through bolus injection. Lomustine (Belustine, 160 mg orally on day 1) was administered.

Panendoscopy with biopsy of the right tonsil was positive for melanoma. Computed tomography of the neck and tonsillar region noted a right lymph node by the subdigastric region, associated with an enlargement of the right tonsil (Fig 1). Computed tomography

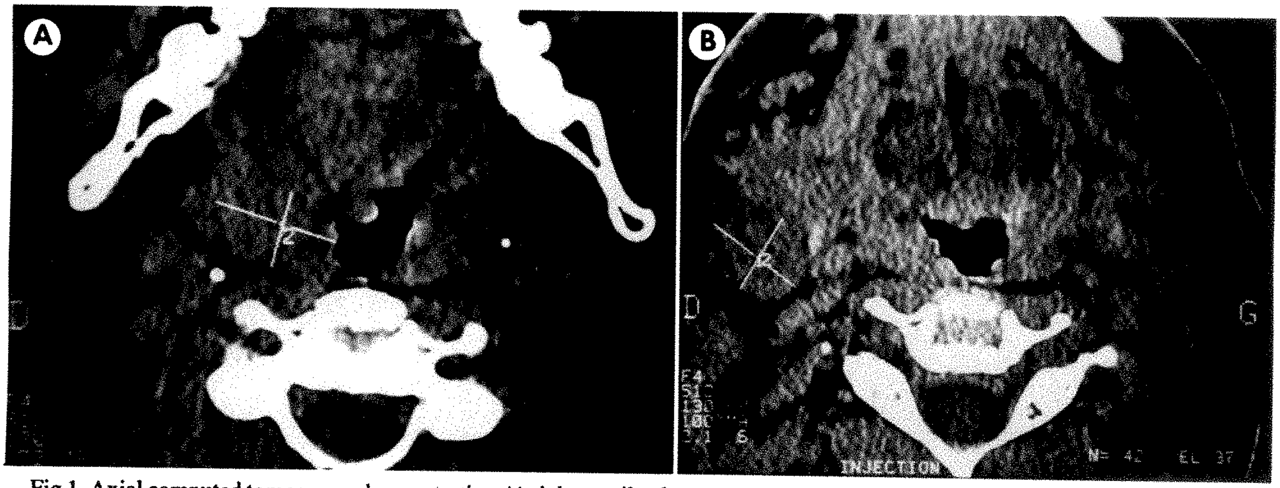

Fig 1. Axial computed tomograms demonstrating A) right tonsil enlargement and B) right subdigastric lymph node enlargement.

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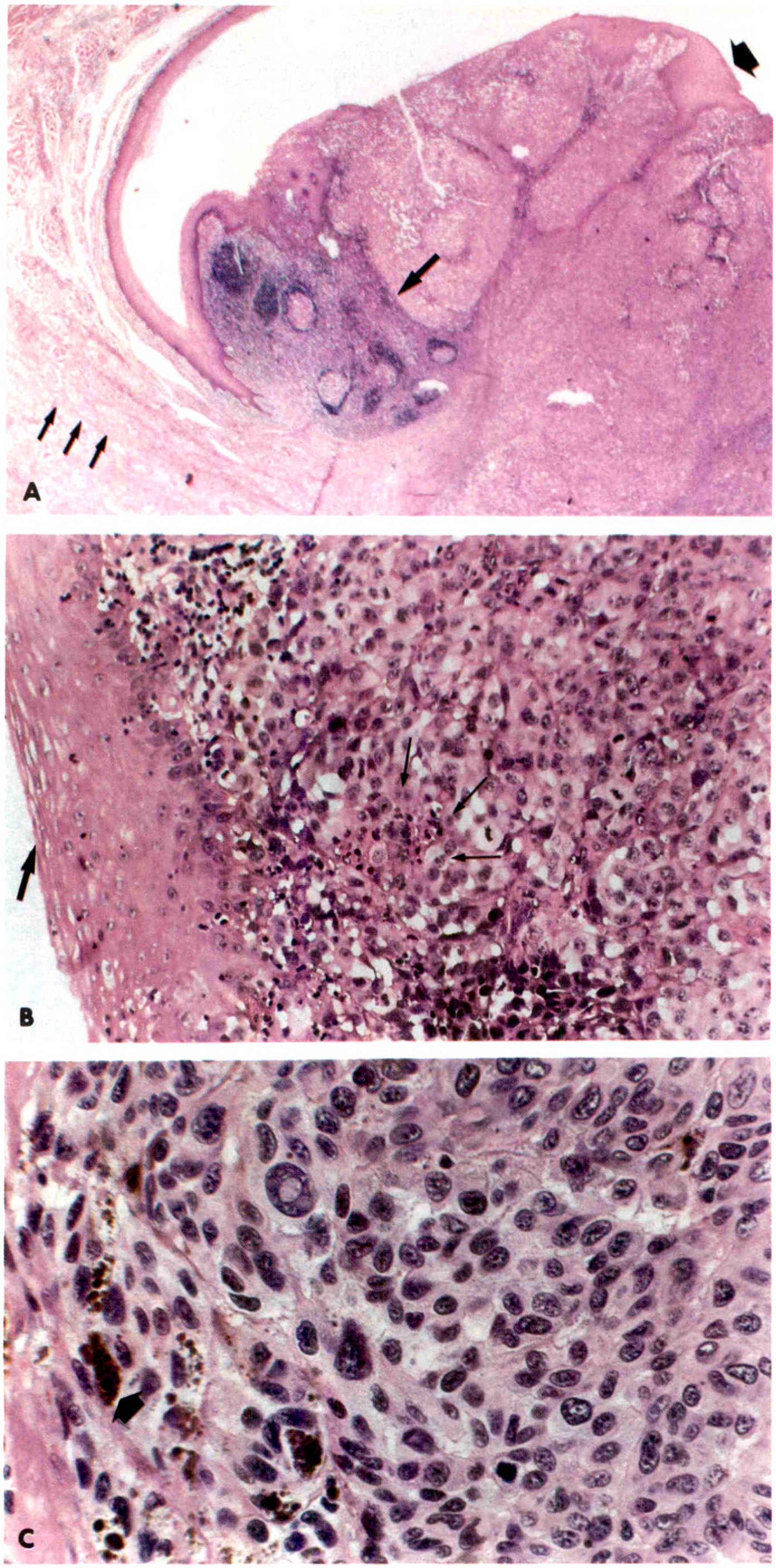

Fig 2. Metastatic melanoma of tonsil. A) Wide arrowhead — tonsil, single arrow — melanoma, multiple arrows — tonsillar pillar (H & E, original x5.5). B) Intact mucosa (single arrow) and melanoma cells (multiple arrows; H & E, original x55). C) Tumor cells staining positive for melanin (H & E, original x105).

of the brain and trunk yielded unremarkable findings. The right thigh and the inguinal region were free of disease. Treatment involved chemotherapy and surgery. Four courses of chemotherapy were delivered. Fotemustine (100 mg/m^2 on days 1 and 8), dacarbazine (Deticene, 250 mg/m^2 on days 14 and 15), and vindesine sulfate (Vindesine, 2 mg/m^2 on days 14 and 15) were delivered through bolus injection. Surgery was an electroresection of the tonsillar region via an oral approach, associated with a radical neck dissection.[18] The postoperative course was uneventful. The margins of resection were free of tumor (Fig 2A,B). Stains were positive for melanin (Fig 2C). Lymph node invasion without extracapsular spread was present. The patient remained asymptomatic 18 months after surgery at the level of the head and neck, but nodal recurrence located by the right thigh was noted at our last examination.

DISCUSSION

The incidence of malignant cutaneous melanoma is rising. In 1987, Schwartz et al[19] reported that the incidence of malignant cutaneous melanoma had doubled during the past decade. The current risk is reported to be 1 in 128, and has been estimated to be 1 in 90 by the year 2000.[20] In contrast, mucosal melanomas of the upper aerodigestive tract are infrequently encountered. Hormia and Vuori,[21] in a series based on 7,253 cases of primary malignancy of the mucous membranes of the upper respiratory and gastrointestinal tracts, reported only 11 melanomas. Henderson et al,[14] in a series based on 8,823 cutaneous malignant melanomas, reported a 0.6% incidence of metastatic mucosal melanoma of the upper aerodigestive tract. To our knowledge, fewer than 100 cases of metastatic mucosal melanoma of the upper aerodigestive tract have been reported in the English-language literature.[1-16] The tonsil and the tongue are the main sites involved, accounting for more than half of the reported cases.[5,8,10,11,14,16] Twenty-two cases of tonsil metastasis from a cutaneous malignant melanoma have been reported.[5,8,10,11,14,16] The other reported sites are the nasopharynx, larynx, lip, pharyngeal wall, gingiva, nasal cavity, pyriform sinus, palate, and maxillary sinus.

In the determination of primary as opposed to metastatic tonsil melanoma, the history of a previous melanoma may be considered, although multiple primary growths might occur. The tonsil is rarely involved by primary melanoma; in the series of Hormia and Vuori[21] none of the 11 primary mucosal melanomas involved the tonsil. Henderson et al,[14] in the single largest series of metastatic melanoma to the tonsil (16 cases), underscored that primary and secondary melanomas of the upper aerodigestive tract mucosa mimic each other clinically and require microscopic examination for their differentiation. Metastatic melanomas are typically covered by an intact mucosal layer,[3,14] as demonstrated in Fig 2A,B. Furthermore, the histopathologic presence of junctional changes in the overlying or adjacent lateral mucosa is a classic clue to primary melanoma.[14,22] However, in the case of a mucosal melanoma, such a feature might be absent because of ulceration or necrosis.

The discovery of mucosal metastases in the upper aerodigestive tract indicates widespread dissemination of a malignant cutaneous melanoma. All of the patients in the series of Henderson et al[14] died of uncontrolled disseminated disease, regardless of the mode of treatment. This poor prognosis is confirmed in our case, which presented an inguinal lymph node recurrence while the tonsillar and cervical regions appeared free of disease 18 months after treatment.

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THIRD INTERNATIONAL SYMPOSIUM ON MENIERE'S DISEASE

The Third International Symposium on Meniere's Disease will be held October 20-23, 1993, in Rome, Italy. For information, contact Kugler Publications bv, Congress Department, PO Box 1498, New York, NY 10009-9998; telephone (212) 477-1970; fax (212) 477-0181.

Ann Otol Rhinol Laryngol 102:1993

IMAGING CASE STUDY OF THE MONTH

CRICOID CALCIFICATION MIMICKING AN IMPACTED FOREIGN BODY

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INTRODUCTION

Ingestion of a foreign body of food origin is a common otolaryngologic problem in Asian countries.[1,2] A swallowed bone may impact in the tonsils, base of tongue, pyriform fossae, or any region of the upper esophagus. The cricopharyngeus, which is the first sphincter in the digestive tract, is one of the sites in which a swallowed foreign body may frequently impact. Because a foreign body impacted at the cricopharyngeus is not visible on indirect examination with a mirror, lateral soft tissue radiography of the neck is the single most important technique used to detect a foreign body in the cricopharyngeus or the cervical esophagus. Calcification of the airway cartilages may masquerade as a foreign body in the digestive tract in some patients with a history of foreign body ingestion. This process may cause confusion to the clinician, who then has to rely on other investigations to exclude the possibility of an impacted foreign body.[3-6]

CASE REPORT

A 50-year-old man complained of severe throat pain at the level of his thyroid cartilage after swallowing a fish bone during his lunch on the same day. Clinical examination did not reveal any foreign body in his oropharynx or hypopharynx. Palpation of his larynx did not cause any tenderness. Radiography of his neck in the lateral view revealed a linear opacity posterior to the calcified cricoid cartilage. This linear opacity was not continuous with the cricoid cartilage calcification (Fig 1). It was determined that the patient had an impacted foreign body at the level of his cricopharyngeal sphincter. He was admitted for rigid esophagoscopy under general anesthesia to remove the ingested foreign body. At esophagoscopy, no foreign body was found and no mucosal lesion was seen. The procedure was terminated and the patient was returned to the ward for observation.

On the following day, the patient still complained of pain at the thyroid cartilage level. Repeat lateral neck radiography showed the same linear opacity. The possibility of a foreign body embedded in the hypopharyngeal mucosa could not be excluded. A computed tomography (CT) scan of the hypopharynx demonstrated a densely calcified ridge on the posterior lamina of the cricoid cartilage (Fig 2). No foreign body was shown on the CT scan.

The patient was observed in the ward. He was able to eat normally. There was no symptom or sign suggestive of infection due to perforation of the digestive tract by any ingested foreign body. The

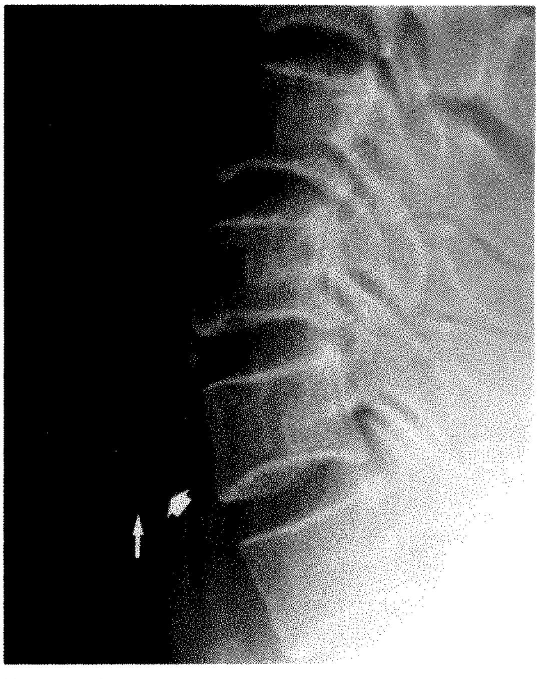

Fig 1. Plain lateral neck radiograph showing calcified ridge on cricoid posterior lamina appearing as linear opacity (wide arrow) separated from rest of cricoid calcification (narrow arrow). This linear opacity mimics ingested foreign body impacted at cricopharyngeus.

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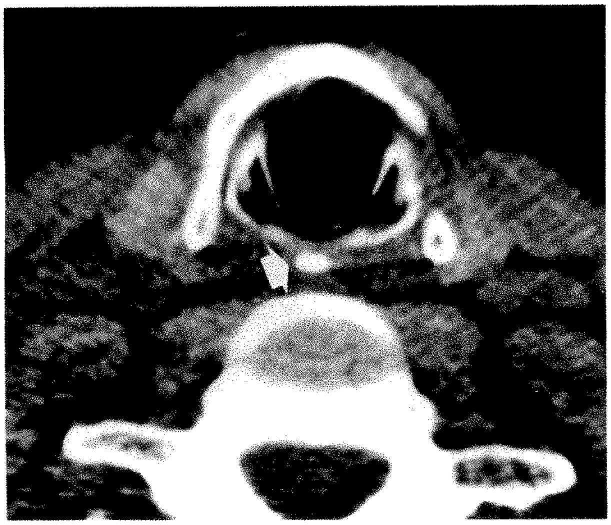

Fig 2. Computed tomography scan of cricoid showing dense calcification of ridge (arrow) on cricoid posterior lamina continuous with rest of cricoid calcification. No foreign body is demonstrated.

patient's pain resolved later in the day and he was discharged from the ward. At follow-up 2 weeks later, the patient was well and had no complaint.

DISCUSSION

The airway cartilages undergo calcification progressing to ossification as part of the aging process beginning as early as in the third decade of life.[7] The degree of calcification increases with age. In the thyroid cartilage, calcification begins in the posteri-or-inferior part and spreads to the rest of the structure. In the cricoid cartilage, calcification starts in the posterior lamina and advances anteriorly along the arches.[8] In some people, the calcification in the ridge on the posterior lamina of the cricoid cartilage is rather dense and on a plain lateral neck radiograph may appear as a linear opacity separated from the rest of the cricoid calcification,[3-5] but a CT scan of the cricoid cartilage does not show this break between the densely calcified ridge and the rest of the calcified posterior lamina (Figs 1 and 2).

This linear cricoid classification seen on a plain lateral neck radiograph can mimic an impacted foreign body because it has the same radiodensity as an ingested bone impacted at this site.[4,5] The clinician and the radiologist must be aware of this normal radiographic feature on a plain lateral neck radiograph and should not mistake it for an impacted foreign body. The linear cricoid opacity is usually thin and does not extend beyond the upper or lower cricoid borders. In contrast, the linear opacity of a foreign body may extend beyond the cricoid borders and may be irregular, depending on the shape of the foreign body (Fig 3). However, if the symptoms and signs are highly suggestive of an impacted foreign body in the hypopharynx, the clinician must prudently exclude the possibility of an impacted foreign body by performing endoscopy or a CT scan.

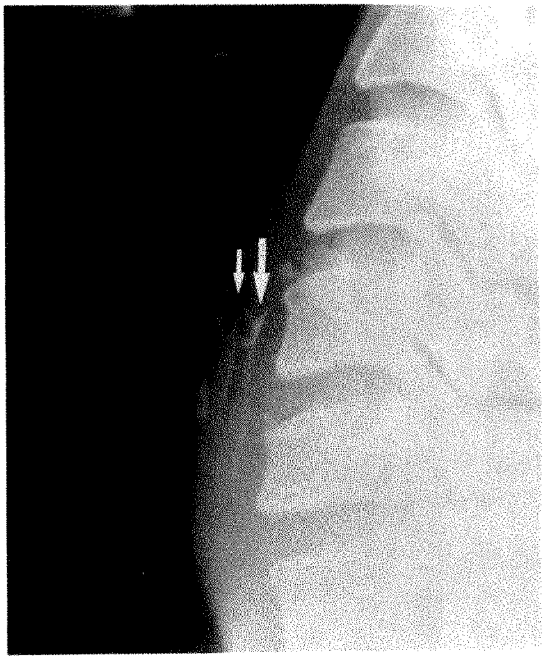

Fig 3. Plain lateral neck radiograph showing ingested foreign body impacted at cricopharyngeus. It is seen as linear opacity (large arrow) behind calcified cricoid (small arrow). Appearance is similar to that in Fig 1.

CONCLUSION

A densely calcified ridge on the posterior lamina of the cricoid cartilage in some patients may on a plain lateral neck radiograph appear as a linear opacity separated from the rest of the calcified posterior lamina. Occasionally, the clinician and radiologist may misconstrue this linear calcification as a foreign body impacted in the cricopharyngeus, as illustrated in this case report of a patient with a history of foreign body ingestion whose symptoms and signs were suspicious of an impacted foreign body. If it is difficult to determine on a plain lateral neck radiograph whether this linear opacity is a calcified ridge on the cricoid or a foreign body impacted at the cricopharyngeal sphincter, endoscopy or a CT scan is needed for further clarification.

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FOURTH INTERNATIONAL SYMPOSIUM AND WORKSHOPS ON INNER EAR MEDICINE AND SURGERY

The Fourth International Symposium and Workshops on Inner Ear Medicine and Surgery will be held July 17-24, 1994, in Snowmass-Aspen, Colorado. For more information, please contact I. Kaufman Arenberg, MD, Executive Director and Program Chairman, 300 E Hampden Ave, Suite 401, Englewood, CO 80110; phone (303) 788-4320 or (303) 850-9545; fax (303) 788-4234.

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PATHOLOGY CONSULTATION
NONNEOPLASTIC VASCULAR LESIONS OF THE MIDDLE EAR

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Nonneoplastic vascular lesions in the middle ear may be arterial or venous. For the former, ectopic location of the internal carotid artery is the most common; a high jugular bulb is the most common venous abnormality. Both may be clinically misdiagnosed without radiographic studies and, in the event, lead to disaster.

Nonneoplastic vascular lesions of the middle ear are, happily, not often seen by surgical pathologists. The lesions, in the form of vascular anomalies, are, however, important considerations in the clinical differential diagnosis of a mass in the middle ear. Inadvertent instrumentation or surgery can lead to disastrous consequences, eg, hemorrhage or neurologic sequelae.

An experienced otologist may be able to distinguish the principal vascular lesions of the middle ear by their color and location, but computed tomography, angiography, and magnetic resonance imaging are diagnostic requirements.[1-4]

The vascular lesions include an ectopic course of the internal carotid artery, aneurysm of the artery, persistence of the stapedial artery, a high jugular bulb, varices of the tympanic membrane, and "hemangiomas" of the middle ear. All are uncommon to rare. As for hemangiomas, the senior author (J.G.B.) has seen only 1 in over 30 years. So-called hemangiomas are nearly always misdiagnosed paragangliomas or exuberant granulation tissue.

The Table, adapted from Mafee et al,[4] presents a comparison of the frequency of neoplastic and nonneoplastic lesions of the middle ear from a survey of 100 patients with these disorders.

ARTERIAL ABNORMALITIES

According to Sinnreich et al,[5] the least common vascular abnormalities of the temporal bone are those affecting the arterial system. These nearly always involve the internal carotid artery or the embryologically related (stapedial) arteries.

In its normal adult course the internal carotid artery lies close to the tympanic cavity and the eustachian tube, where it is usually well covered with bone, albeit often thin. The artery enters the petrous bone through the carotid canal, just medial to the styloid process. It then rises vertically and anterior to the tympanic cavity and bends sharply anterior and medial, passing inferior to the eustachian tube. After passage through the foramen lacerum, the artery enters the cranium at the junction of the petrous apex and basisphenoid.

An aberrant location, aneurysmal dilation, and persistence of the embryonic stapedial artery are the 3 principal arterial abnormalities presenting in the middle ear.[2,6,7]

The incidence of stapedial artery remnants varies from 1 in 5,000 to 1 in 10,000 routine stapedectomies.[7] A significant size to the remnant is rare.[7]

Aneurysms of the petrous portion of the internal carotid artery are equally rare. They may be congenital or acquired (secondary to trauma or infection).[7]

By 1993 approximately 45 examples of an aberrant internal carotid artery in the middle ear had been reported.[2] There is usually no other associated abnormality. The aberrant presentation occurs most often in women and on the right side; bilaterality is very unusual. The mean age at time of diagnosis is 25 years.[2]

Symptoms include a pulsatile tinnitus, vertigo, and a progressive loss of hearing. Physical findings cover a wide range, from those usually associated with chronic otitis media or cholesteatoma to a reddish blue, pulsatile retrotympanic mass, usually in the lower segment of the eardrum. There may also be a deceptive absence of findings.

The underlying mechanisms of the aberrance of the internal carotid artery are unclear, but any one of

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NEOPLASTIC AND NONNEOPLASTIC LESIONS OF THE MIDDLE EAR AND MASTOID

	No. of Patients
Neoplasms	
Paraganglioma	28
Primary neurogenous tumors of facial nerve	6
Secondary neoplastic involvement of facial nerve	5
Intratemporal meningioma	5
Extension of acoustic neuroma	2
Labyrinthine schwannoma	2
Adenomatous tumors of middle ear (adenoma)	2
Adenocarcinoma of middle ear	2
Inverted papilloma of middle ear cleft	1
Fibromyxoma	1
Hemangiopericytoma	2
Multiple myeloma	2
Leukemia	1
Metastases	4
Extension from carcinoma of external canal	4
Aggressive fibromatosis	1
Nonneoplastic lesions	
Exposed and bulging jugular bulb	9
Extension of primary cholesteatoma from petrous apex	5
Cholesterol granuloma of middle ear	5
Ectopic internal carotid artery	4
Extension of cholesterol granuloma from petrous apex	2
Posttraumatic facial nerve fibrosis	2
Posttraumatic internal carotid artery aneurysm	1
Wegener's granulomatosis	1
Tuberculoma of middle ear	1
Nontuberculosis granulomatous inflammation of middle ear and mastoid	2
Total	100

Adapted from Mafee et al.[4]

the following may be at work: 1) a traction deviation of the artery by an anomalous branch of the stapediohyoid artery, 2) an abnormal anastomosis between the inferior tympanic artery and the caroticotympanic artery, 3) dehiscence of the thin bony plate between the artery and the tympanic cavity, 4) an abnormally placed carotid canal, or 5) carotid duplication (fenestration) of the artery.[2,6,7]

VENOUS ABNORMALITIES

A confluence of the sigmoid and inferior petrosal sinuses forms the jugular bulb. The bulb's anatomy is quite variable, with the left bulb usually smaller than the right. The bulb not infrequently extends above the inferior rim of the bony annulus, with or without a bony covering. Normally, a high jugular bulb is covered by bone. Graham[8] has indicated that 6% of the bulbs extend above the inferior rim and that a similar number show a dehiscence in the bony floor of the middle ear cavity covering the jugular bulb.

A small jugular bulb is separated from the middle ear by usually compact bone and is in close relationship to the internal carotid artery with cranial nerves IX, X, and XI in between. If the bulb is large it can extend into the mesotympanum with a thin or dehiscent bony covering — both placing the bulb at risk of injury during instrumentation in the middle ear or even at myringotomy.

The definition of a high jugular bulb ranges from extension to or above the inferior tympanic annulus (5% to 10% incidence) to a placement of the jugular bulb's dome within 2.0 mm of the inferiormost limit of the internal auditory meatus (63% frequency in adults and adolescents).[9] The latter situation is particularly relevant to neurotologic surgery of the posterior fossa.[9]

High jugular bulbs are most often asymptomatic, but they can cause tinnitus or conductive deafness by blocking the round window niche or interference with the ossicular chain. Encroachment on structures of the inner ear can also occur.

Radiographs show several variations of the high jugular bulb: 1) the jugular fossa and bulb are high and the soft tissue extending into the middle ear is covered by a thin bony rim, 2) the fossa and bulb are high and there is an incomplete shell of bone over the soft tissue projection into the middle ear, or 3) the jugular bulb herniates through a large defect in the dome of the normally situated jugular fossa.[10]

The differential diagnosis of the vascular anomalies always includes paraganglionic (glomus jugulare, glomus tympanicum) tumors and vascularized cholesterol granulomas. The tympanic membrane is usually intact, and microscopic otoscopy may give clues.[11] An ectopic internal carotid artery tends to be a reddish blue mass lying in the inferior mesotympanum in contact with the medial surface of the tympanic membrane. The high jugular bulb has a bluish color and lies in the posterior part of the middle ear. The paragangliomas lie more toward the middle of the mesotympanum. The clinical implications are such that radiographic studies (see above) are requirements.

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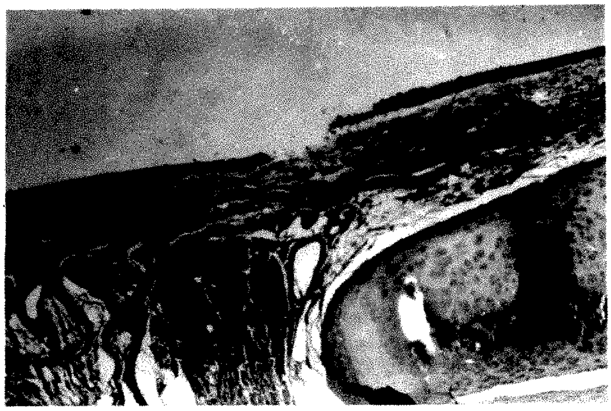
EXTRACRANIAL OPTIC NERVE DECOMPRESSION

A meeting to discuss extracranial optic nerve decompression as a treatment for traumatic optic neuropathy will be held November 6-7, 1993, at Massachusetts Eye and Ear Infirmary, Boston, Massachusetts. For information, contact Michael Joseph, MD, Massachusetts Eye and Ear Infirmary, 243 Charles St, Boston, MA 02114-3096; telephone (617) 573-3192; fax (617) 573-3914.

LETTERS TO THE EDITOR

To the Editor:

We enjoyed reading the article "Laryngotracheal Reconstruction in Adults With the Sternocleidomastoid Myoperiosteal Flap" by Friedman and Mayer *(Ann Otol Rhinol Laryngol* 1992;101:897-908), detailing the results on 26 cases of airway reconstruction. We first described this technique 10 years ago for the repair of the disrupted laryngotracheal tract[1] and have continued to use it through the years. Our preliminary assumption was that the periosteal flap would generate osteogenesis to furnish a rigid framework resistant to alternating pressure. In an experiment performed on 10 dogs (unpublished data), we did not detect new bone formation after a year at the site of the tracheal reconstruction with the myoperiosteal flap. The defect in all cases was found sealed with a fibrous tissue lined with respiratory epithelium (see Figure). Furthermore, 1 of our patients went into severe respiratory distress when he was decannulated 2 months following a reconstruction of more than one third of the circumference of the airway. Bronchoscopy revealed collapse in the reconstructed area, sustaining our suspicion, later proven by the animal study, that this flap does not necessarily form bone tissue. This is not a problem in cases with defects involving less than 30% of the circumference. What we wish to emphasize is the possibility of collapse in larger defects. We still think that it is worthwhile to fold over the muscle and suture it on the reservoir area to provide more extensive support.



Section of trachea showing cartilage plate (right). Specimen is lined by respiratory epithelium. Area of reconstruction (left) is occupied by fibromuscular tissue and shows no evidence of bone formation (H & E, original x30).

The T-tube modification we suggested[2] simplifies the mechanics of suction and makes frequent changing of this tube redundant during the healing process.

We also think that there is no need to sever the sternal head of the sternocleidomastoid muscle. Its clavicular head can be transferred, medially, to the airway through a tunnel created by finger dissection of the soft tissues behind the sternal head of this muscle. This preserves the normal configuration of the neck.

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To the Editor:

I appreciate the comments from Drs Tovi and Gatot and am aware of their excellent work with the sternocleidomastoid myoperiosteal flap.

I first used the flap for tracheal defects caused by surgical resection to treat thyroid carcinoma. A description of this technique was published in 1980.[1] It was their first published report in 1983, suggesting that bone growth is possible, that prompted us to design an experimental study to determine if bone growth occurs. Our previously published studies showed clinical, radiologic, and histologic evidence of bone growth.[2] Later clinical studies showed computed tomographic evidence of calcified tissue, which we presume to be bone.[3] I am puzzled by Tovi and Gatot's poor results in their experimental study. I do believe that the success of the flaps depends on suturing periosteum, and not muscle, to the defect. Similar histologic sections in our study showed bone growth. The flap is more difficult to elevate in dogs because it is sternal periosteum that is required. Sternal periosteum does not elevate as easily as clavicular periosteum, which is used in humans.

I believe the suggestion to leave the sternal head of the sternocleidomastoid muscle in place is an excellent idea and I may incorporate the modification in future procedures.

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Book Review Editor's Note: From time to time we receive for review books that because of their limited application, juxtaposition to otolaryngology, or a number of other reasons, are worthy of attention, but do not call for a thorough, analytic review. The following 6 books fall into that category.

Manual of Otolaryngology. Diagnosis and Therapy

Marshall Strome, James H. Kelly, and Marvin P. Fried, editors. Second edition. Soft cover, illustrated, indexed, 287 pages, 1992. Little, Brown and Co, Boston, Mass.

This book was prepared for the use of medical students and residents. The authors chose to focus on emergencies in otolaryngology and head and neck surgery. Details of the essentials of otolaryngology and head and neck surgery, along with the most pertinent information, are presented in a concise outline form. Unfortunately, outline forms tend to be monotonous, and there is a constant need to look back to see where the reader is in the outline. The spiral paper binding makes the book easy to manipulate, and it is offered at a conservative price.

Essentials of Otolaryngology

Frank E. Lucente and Steven M. Sobol, editors. Third edition. Soft cover, illustrated, indexed, 594 pages, 1993. Raven Press, New York, NY, $32.

This volume is directed toward medical students, residents, and primary care physicians. The first 4 chapters provide fundamental information about history-taking, anatomy, physiology, and physical examination. The subsequent chapters are based on these. For a concise volume on such a vast subject, the book is reasonably complete. There are 48 chapters, some on such unusual topics as bad breath and itching of the ears, plus appendices on audiology, speech-language pathology, and antimicrobial therapy in otolaryngology (with tables of drugs and dosages).

The Mast Cell in Health and Disease

Michael A. Kaliner and Dean D. Metcalfe, editors. *Lung Biology in Health and Disease*, Series 62. Claude Lenfant, executive editor. Hard cover, illustrated, indexed, 858 pages, 1993. Marcel Dekker, New York, NY, $195.

The editors' goal in preparing this book was to present a comprehensive review of the "latest understanding of the mast cell and related diseases." To do so, they solicited contributors from across the United States, as well as Canada and England. Chapter 11 gives an excellent review on the role of histamine receptors, especially their mediating effects on various organ systems. Included in this essay is a description of the more recent discoveries of the immunocytochemicals and biochemical-opathies, showing that histamine is a neurotransmitter present in nerve endings. The discussion of the effectiveness of antihistamines as antagonists to H1, H2, and H3 receptors is very illuminating.

The mast cell has been studied in a number of diseases, including chronic glomerulonephritis, contact allergy, benign and malignant tumors, urticaria, graft rejection, Crohn's disease, Whipple's disease, ulcerative colitis, scleroderma, rheumatoid arthritis, and others. The participation of mast cells in allergic diseases involves activation of mediator release immunoglobulin E interacting with allergen and histamine-releasing factors and cytokines. It is the understanding of the biology of these factors that is important to the otolaryngologist–head and neck physician, and this book would be a very good reference for those physicians.

Pulmonary Disease in the Elderly Patient

Donald A. Mahler, editor. *Lung Biology in Health and Disease*, Series 63. Claude Lenfant, executive editor. Hard cover, illustrated, indexed, 528 pages, 1993. Marcel Dekker, New York, NY, $155.

In 14 chapters, 25 authors contribute information on such topics as physiologic and anatomic changes in the aging lung, monitors of oxygen delivery and carbon dioxide elimination, smoking cessation in the older chronic smoker, components of a pulmonary rehabilitation program, therapy for respiratory tract infections, cancer of the lung in older patients, nutrition in the elderly patient with pulmonary disease, and others.

This book has no specific application to otolaryngology–head and neck surgery, but should be of interest to the conscientious physician in any field, especially those who care for a large number of elderly patients.

Atlas of Diseases of the Oral Mucosa

J. J. Pindborg. Fifth edition. Hard cover, illustrated, indexed, 399 pages, 1992. WB Saunders, Philadelphia, Pa, $125.

The main emphasis of this atlas is the clinical diagnosis of diseases of the oral mucosa. The text that accompanies the very distinct and realistic photography (taken with a Hasselblad camera) is quite informative. An atlas of this sort, whether it is this or another one, should be available in every patient care facility for immediate consultation.

Skin Endpoint Titration

Richard L. Mabry, editor. AAOA Monograph Series. Soft cover, illustrated, indexed, 96 pages, 1992. Thieme Medical Publishers, New York, NY.

This small monograph is distributed by the American Academy of Otolaryngic Allergy. It is intended to serve as a convenient introduction to skin end point titration. It is also a reference source for that technique. In addition to discussing titration setups, methods, and so forth, it also presents pollen guides, patient information, and some marketing techniques for the physician-allergist. The material is well presented. It is not intended to be the springboard for setting up an allergy practice, but it can be a helpful adjunct in doing so. Even those who do not practice otolaryngic allergy need to comprehend, in general, many of the principles and terms involved to better serve their patients.

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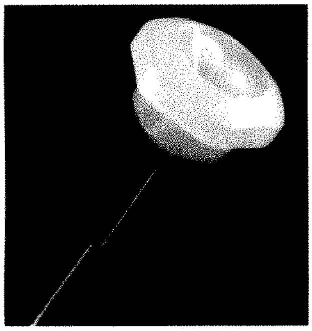

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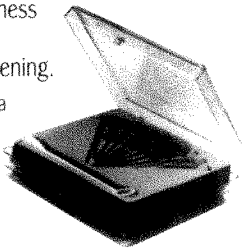

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